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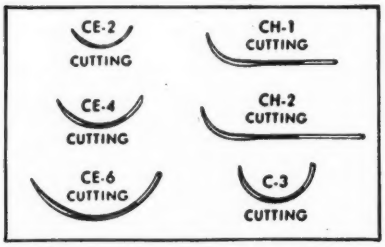

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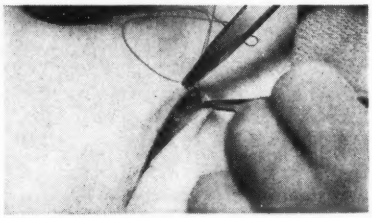

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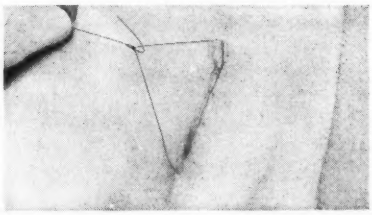

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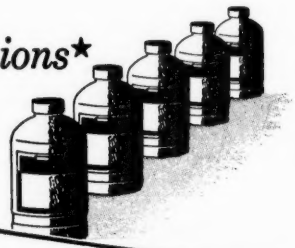

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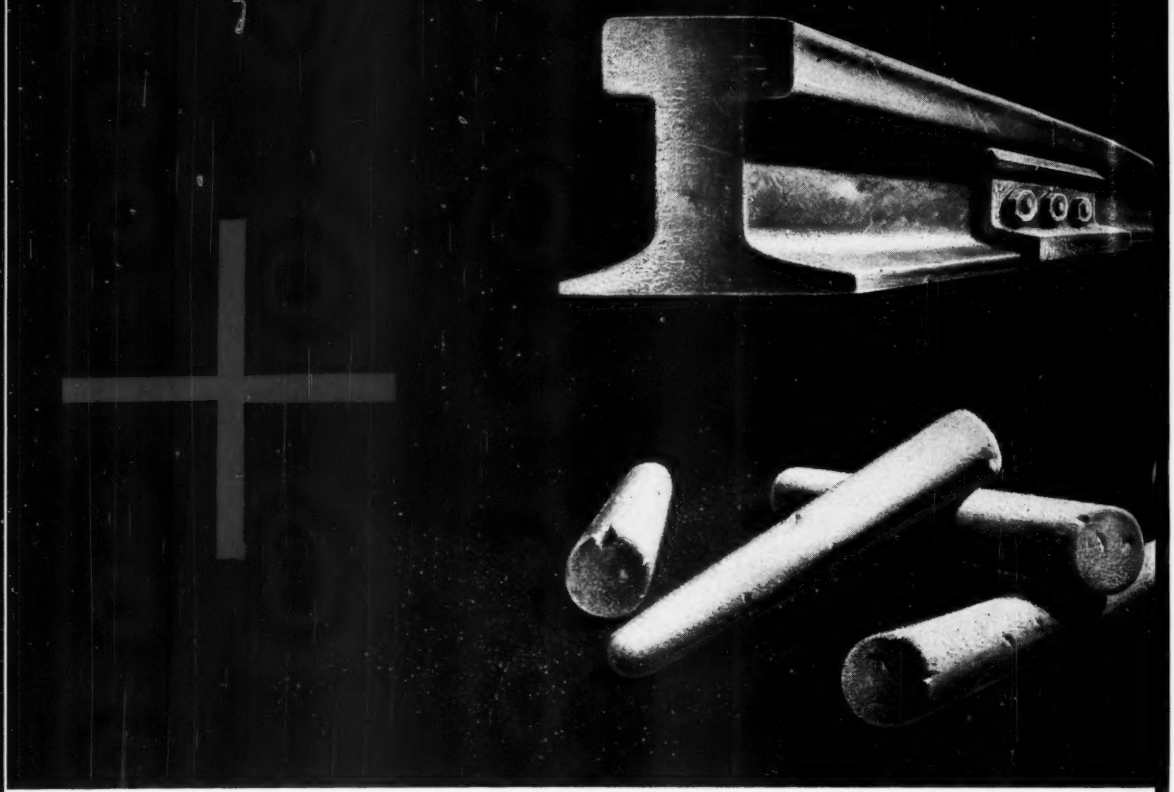

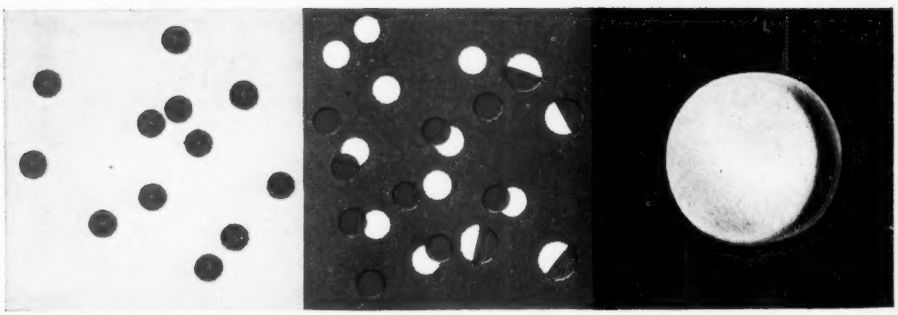

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SURGERY
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FUNCTIONAL VENOGRAPHY OF THE LOWER EXTREMITIES

HARRIS B. SHUMACKER, JR., M.D., F.A.C.S., THOMAS C. MOORE, M.D., and J. A. CAMPBELL, M.D., Indianapolis, Indiana

A CLEAR understanding of certain facets of the pathophysiology of venous disorders of the lower extremities has eluded the most intensive investigative efforts. Although much has been learned, perplexing problems remain. One key to the accurate appraisal of these disorders is concerned with a more precise delineation of the relative importance of the various factors promoting venous return in the face of the gravitational effects of the upright position—and of the hemodynamic alterations produced by pathologic venous changes.

The clinical history and physical examination contribute much useful information, to be sure, but they sometimes fail to present a complete picture of the pathogenesis of the patient's symptoms. Because of the limitations of the routine methods of examination, increasing interest has developed in roentgen studies of the venous system of the lower extremities.

Berberich and Hirsch in 1923 were the first to inject radiopaque material into the veins of humans. In 1936, Barker and Camp employed venography in the study of obstructive venous lesions. Further experience with horizontal lower extremity venography was reported in 1938 by Dos Santos and in 1940 by Bauer (2), and Dougherty and Homans. These studies were primarily anatomic and were directed toward the demonstration of the state of patency of the major venous channels. They were employed principally in the study of thromboembolic disorders.

The introduction of the concept of retrograde venography by Luke (10) in 1941 marked the beginning of efforts to evaluate venous function, as well as anatomy, by roentgen means. His technique was designed to investigate the competency of femoral valves in preventing distal regurgitation of injected radiopaque medium when the femoral vein was temporarily occluded proximal to the site of injection. Initially, he held the impression that the retrograde flow of radiopaque material past one or more valve stations was an indication of deep venous pathology. However, more extensive experience with the use of this method in both abnormal and control cases led him to conclude in 1943 (11) that "it is apparently incorrect to assume that a deep vein which allows retrograde flow is a diseased or congenitally malformed one." Similar findings were reported in 1949 by one of us (14) who likewise noted varying degrees of retrograde flow in apparently normal control subjects when neo-iopax was injected into the femoral vein with the leg dependent. He

From the Departments of Surgery and Radiology, Indiana University Medical Center, Indianapolis. Indiana. Aided by a Contract between the Office of Naval Research, the United States Navy, and Indiana University.

also suggested that the effect of muscle activity on retrograde flow in the dependent limb would provide a more complete functional venographic method.

Bauer (3), in 1948, described a technique of retrograde venography by injection into the proximal end of the greater saphenous vein. The vein was cannulized in the groin surgically under local anesthesia and the vein was ligated distally. He regarded retrograde flow of the radiopaque solution with the patient erect as abnormal, regardless of the presence or absence of symptoms, and advocated ligation of the popliteal vein as the preferred method of surgical management. Sylwan, using percutaneous femoral injection, also concluded that retrograde flow was an indication of a diseased or abnormal deep venous system. A technique similar to that of Bauer was described in 1950 by Starkloff, Bricker, McDonald, and Litzow.

Robertson, Share, and McGovern, in 1949, suggested more distal injection for the study of retrograde flow in the leg. They employed cutdown cannulization of the lesser saphenous vein in 6 patients and injected diodrast through a No. 8 ureteral catheter which had been passed up the vein a distance of approximately 15 centimeters. This technique was modified in 1951 by Ferreira, Villamil, and Ciruzzi who added the use of muscle contractions after the initial injection of radiopaque material. Scott and Roach in 1951 reported experiences with the injection of a radiopaque solution into a foot vein with a tourniquet about the ankle and the lower extremity dependent and quiet. Boyce, Detar, and Vest have recently used the veins of the penis for obtaining quiet dependent venograms, a technique which often affords delineation of both femoroiliac veins and certain other pelvic veins. Like Bauer, Sylwan, and others, they interpreted retrograde passage of the radiopaque solution as indicative of valvular incompetence.

Since the initial suggestion to use muscular activity to supplement the information gained from retrograde dependent venography was made from our institution in 1949, continued investigations have been carried out to evaluate various techniques of functional venography in both symptomatic and control patients. It is the purpose of this communication to present the results of these additional studies.

That such studies were needed and offered considerable promise was evident. Venographic studies carried out after proximal femoral vein injection with the extremity dependent and at rest were confusing and their interpretation extremely difficult. Retrograde flow down the limb had been generally interpreted as evidence of pathologic regurgitation and, in the opinion of some, had served as a clear indication for ligation of the venous trunk. On the other hand, Luke had called attention to the fact that in some individuals, without symptoms and with presumably normal venous circulation, there was passage down the femoral vein of a radiopaque solution when it was injected into the vein during proximal occlusion, and one of us had described retrograde flow in similar cases when radiopaque material was introduced into the unobstructed femoral vein of the dependent limb. Following these initial observations, a large series of patients without symptoms or signs of venous disease, but requiring intravenous pyelography, was studied by injecting the dye into the femoral vein with the extremity in quiet dependency (6). It was obvious from this study that, under such conditions, varying degrees of regurgitation of the opaque solution occurred in a significant percentage of cases.

Some difference of opinion existed among the authors as to the explanation of this phenomenon. One of us felt that it was necessary to disregard such retrograde flow as evidence of venous dysfunction in all patients since it could be observed in normal as well as in obviously disordered extremities. One of us felt initially that this regurgitation had to be considered evidence of incompetent valves and that incompetence of valves in the deep circulation might, or might not, be associated with symptoms of venous stasis just as is the case with superficial varicosities. In attempting to understand this puzzling problem more adequately, two factors seemed of possible significance. For one thing, one had to consider the fact that the injected radi-

opaque solution is heavier than blood and might conceivably pass down through the valve even if blood should not. Considering the hydrostatic pressure of the column of blood in the dependent vein, however, it appeared unlikely that the slightly heavier weight of the solution would break the competency of normal valves. A second factor was thought to be of real importance, namely, that the studies had been made with the extremity in a state of quiet dependency. It has long been known that contraction of large muscle masses is of extreme importance in facilitating venous return. The question could be legitimately asked whether normal veins in the quiet, dependent limb could become sufficiently distended as to render certain valves incompetent.

As a consequence of these considerations, the effect of muscular activity upon dependent venography has been investigated. The present observations are based upon 115 separate venographic studies before and after exercise of the dependent limb. They include venographic studies upon 23 presumably normal individuals without signs or symptoms of venous disorder. The remainder were made in patients with symptoms or signs suggesting definite or possible disturbance of the venous circulation. They do not include a previous large experience with quiet dependent femoral venography in normal subjects and in individuals with various venous disorders.

OBSERVATIONS IN CONTROL SUBJECTS WITHOUT APPARENT VENOUS DISORDER

Femoral venography. Ten individuals ranging in age from 23 to 92 years had venography performed in the following way: They were placed supine on an x-ray table with a foot rest and were tilted 60 degrees with the feet down. A 7 by 17 inch film was placed under the thigh and lower portion of the pelvis and a second film of the same size under the leg and knee. After infiltration with ½ per cent procaine solution, a No. 18 needle was introduced percutaneously into the common femoral vein just below the inguinal ligament and 30 cubic centimeters of 35 per cent diodrast or 50 per cent neo-iopax was injected in a leisurely fashion. Exposure of the film was made immediately after the conclusion of the injection using ordinary soft tissue technique. While the films were being removed and replaced, the patient was urged to exercise vigorously by raising himself on his toes for 10 times. A second exposure was then made, approximately 1 minute after the first.

Three demonstrated opacification of the common femoral vein only down to the first or second valve station, while significant regurgitation was observed in 7: in 1 to the midthigh, in 4 into the lower thigh, in 1 to the knee (Fig. 1), and in 1 to the midleg. In all cases, after exercise, the superficial and profunda femoral veins were completely or nearly completely emptied of radiopaque material though often small amounts of medium could be seen hanging in the valve cusp areas and occasionally small branches were still faintly opacified.

Although retrograde passage of the injected material from the femoral vein occurs commonly in quiet dependency, it is propelled normally toward the heart with exercise.

Popliteal venography. Ten subjects ranging in age from 16 to 73 years were subjected to popliteal venography. The procedure was quite like that described in the preceding section except that the patient was in the prone position with the table tilted 60 degrees and the injection was carried out percutaneously in the popliteal space. The initial exposure was made immediately following injection of the radiopaque material and the second 1 minute later, following the same type of exercise as used in femoral venography.

In all instances the femoral and popliteal veins were clearly opacified in the first films. In all of them a varying regurgitation into the deep veins of the legs was noted. In some only one or more of the deep leg veins was opacified (Fig. 2), while in others retrograde flow into numerous deep leg veins occurred. With exercise the opaque material cleared from the deep veins in all, either completely except perhaps for a small residuum in the valve areas, or almost completely.

This type of functional popliteal venography clearly outlines the femoral and popliteal veins. A varying amount of regurgitation into the deep veins of the leg is likely to occur.

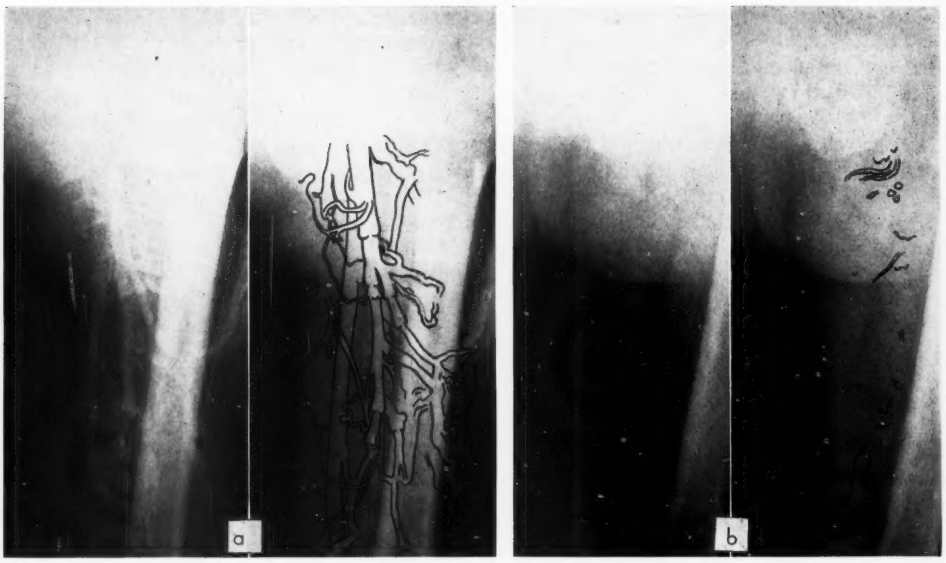

Fig. 1. Retrograde dependent femoral venogram in normal 23 year old subject, a, before and, b, after exercise. In a the marked regurgitation down the superficial and profunda femoral veins is seen, and in b clearing except for a small amount of radiopaque material hanging in the valve areas and in some small branches. No opacification of the deep vessels of the leg was seen in either film. In this and all subsequent figures a retouched photograph is shown alongside the untouched photograph. It was impossible to obtain photographs which delineated the opacified veins as well as the x-ray films themselves. In order to add to the clarity of interpretation all veins visualized on the x-ray film, regardless of the degree of opacification, were outlined with ink on the photograph.

With adequate exercise the deep venous system propels the contrast medium proximally toward the heart.

Superficial venography. Three control subjects varying in age from 63 to 78 years were examined venographically following percutaneous injection of radiopaque medium into a superficial vein around the knee area or on the dorsum of the foot. The patient was either prone or supine, depending upon the vein used, and the table was tilted downward 60 degrees. The method of exposure and exercise was the same as previously described.

The superficial as well as the deep venous system was visualized in all cases. The films made after exercise showed in general diminished opacity of the veins, indicative of proximal passage of the injected solution (Fig. 3). If clearing were incomplete, proximal movement of the material was evident since clearing was most complete in the veins of the leg and least in the proximal portion of the femoral vein.

In normal subjects, injection of radiopaque material into a superficial vein is followed by opacification of the deep and superficial venous systems with evidence of proximal propulsion of the contrast medium in both systems with exercise.

OBSERVATIONS IN PATIENTS WITH SIGNS AND SYMPTOMS OF VENOUS STASIS OR LYMPHATIC BLOCKADE

Ninety-two functional venographic studies were carried out on patients with suggestive evidence of venous stasis or, in 1 case, of lymphatic blockade. In some of the cases the patient's difficulties appeared to be due to simple varicose veins and in others there was a clear history of deep venous thrombosis. A few of them had previously suffered one or more episodes of pulmonary embolism. In a small number of cases with stasis ulcers in the area just above the medial malleolus the history and physical examination failed to give any substantial clues to the cause of the

Fig. 2. Control dependent popliteal venogram in a 27 year old subject, a, before and, b, after exercise. The normal filling of the femoral and popliteal veins with some retrograde flow into the leg is seen in a with clearing except for a small amount of radiopaque material in the valve areas after exercise, b.

patient's trouble. In a few patients, considerable edema of the lower extremity was encountered without demonstrable venous, cardiac, or renal pathology. One patient had had superficial femoral ligation and division 3 years before her examination.

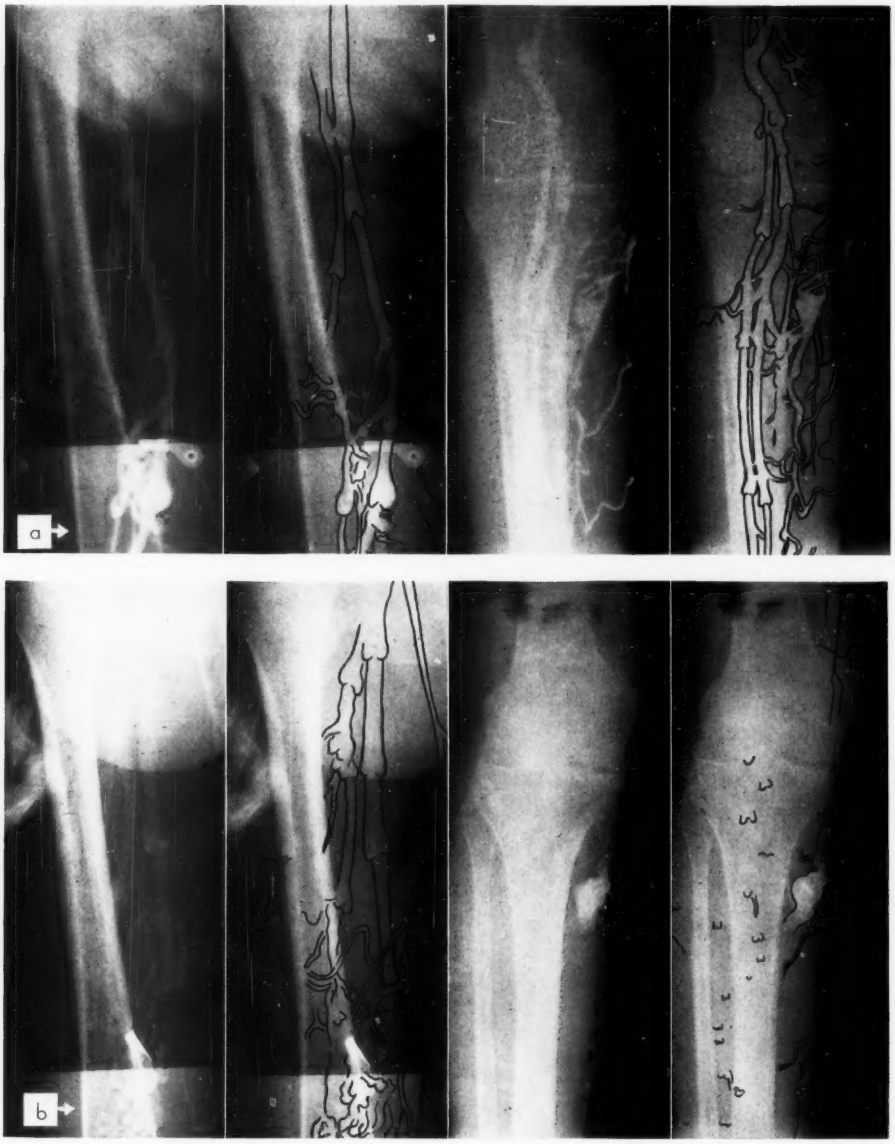

Fig. 3. Control dependent superficial venogram in a 78 year old individual following injection into a superficial vein just below the knee, a, before, and, b, after exercise. In the initial films, the superficial and deep veins are clearly outlined. Regurgitation has occurred in the deep veins of the leg. In b, it is seen that marked clearing has occurred. The incompleteness of clearing is probably due to the inadequacy of exercise resulting from the age and weakness of the patient.

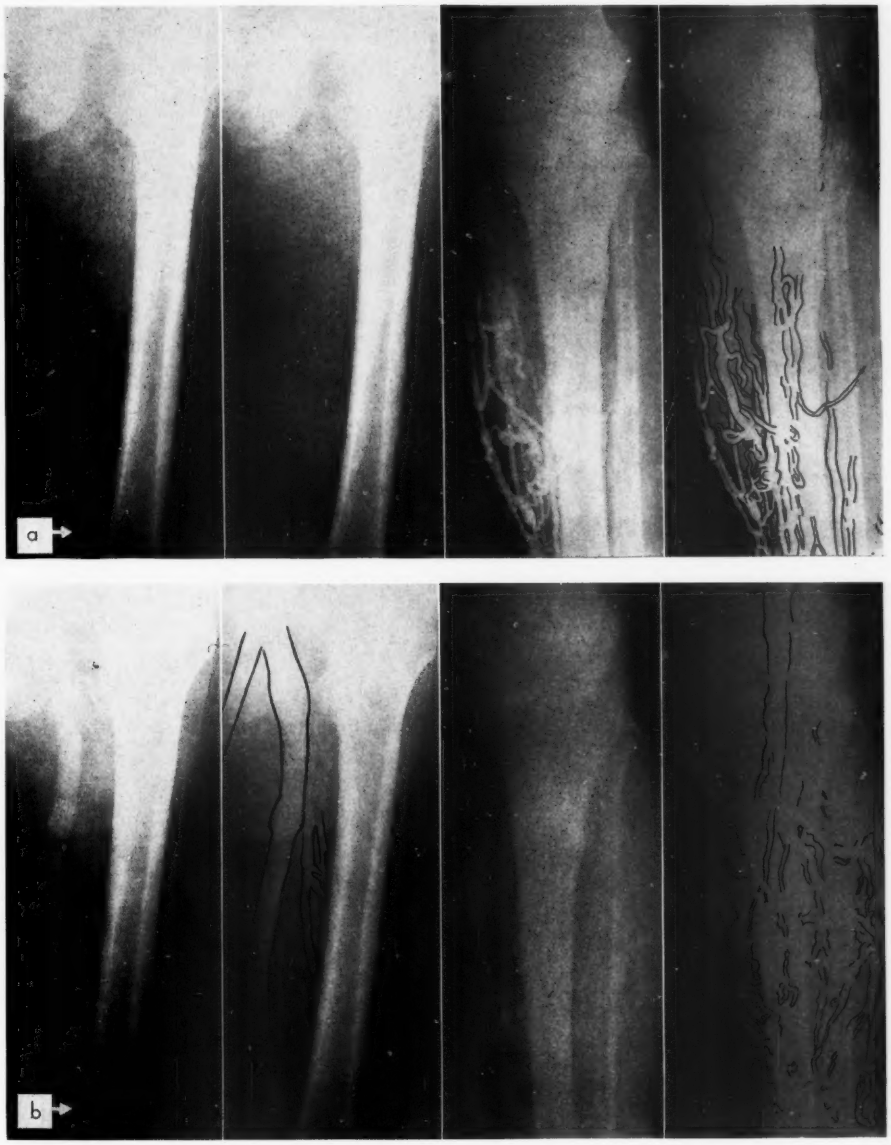

Fig. 4. Functional superficial venograms in case of varicosities of major saphenous system. The opaque solution was injected into the saphenous vein below the knee. The resting dependent films, a, show regurgitation distally down varices with beginning filling of the deep veins of the calf. After exercise the femoral and popliteal veins are visualized, b. There is visualization of the main saphenous vein, most densely opacified near where it unites with the common femoral. The varices in the leg are more diffusely but less densely opacified.

In the majority of the patients the injection was carried out at only one site, either into the femoral vein in the groin, into the popliteal vein, or into one of the superficial veins of the thigh, leg, or foot. In a few patients, however, injection was performed, on separate days, at more than one location in the hope of gaining additional information.

Varicose veins. The patients with superficial varicosities were studied largely by superficial injection, popliteal injection, or both. When injection was made into one of the superficial varices, the radiopaque solution drifted downward, filling the more distal varices and entering the deep circulation through communicating channels. Sometimes the popliteal and femoral veins were filled at the time of the first exposure during quiet dependency and sometimes they were filled only after exercise. The bulk, if not all, of the contrast medium which was returned proximally toward the heart was transported in the deep circulation. There was no real evidence of proximal return in the superficial venous system either with exercise or in quiet dependency. The distended varices, following exercise, were more diffusely, but less densely opacified—due partially, no doubt, to the dilution of the injected solution and partially to the proximal passage of a significant portion of it in the deep circulation. In some cases, the second film showed evidence of what might be interpreted as regurgitation down the greater saphenous vein from its junction with the common femoral.

The findings in 2 illustrative cases of superficial varicosities studied by superficial injection will be presented briefly. The first patient, a 45 year old former restaurant operator, had suffered from bilateral superficial varicosities for years. He had had stasis ulcers and considerable leg pain. Injection was made into the saphenous vein just below the knee (Fig. 4). The second patient was a 49 year old farmer who had had varicose veins for 30 years. Although there was no history of ulceration in this case, examination revealed pigmentation, dermatitis, and some induration in the areas above both medial malleoli. The radiopaque solution, in this case, was injected into the saphenous vein above the knee (Fig. 5). In both cases the injected solution drifted downward in the varices and passed through communicating veins into the deep circulation. In one, following exercise, the contrast material was seen to be in transit through the femoral and popliteal veins. In the other, the postexercise roentgenogram showed intensification of opacification of the femoral and popliteal veins on one occasion, while on another these veins were filled at the time of the initial exposure and had cleared by the time the postexercise film was made. In both cases the varices of the leg were more diffusely but less densely opacified after exercise. Opacification of the upper end of the great saphenous vein during proximal passage of the contrast material through the common femoral vein was noted.

When popliteal vein injection was carried out in cases of superficial varicosities, the radiopaque solution filled the popliteal and femoral veins. Regurgitation into the varices of the leg was often encountered (Fig. 6). After exercise the deep venous system was cleared with proximal passage of the material. Varying amounts of contrast medium remained in the varices, which were more diffusely but less densely opacified as was the case when the injection was made into the superficial system.

Deep venous alterations following thrombotic occlusion or ligation. All of the patients with clear or suggestive histories of deep venous thrombosis were studied by popliteal injection. In a small number of them femoral injection was also carried out. The popliteal vein was found to be patent in all of the patients studied. Furthermore, varying degrees of recanalization of the popliteal-femoral vein were encountered in all of them. These veins were opacified and had a moth-eaten appearance. The valves could not be identified. Numerous collateral veins in the thigh were frequently visualized. On exercise, the recanalized veins cleared, and all of them were able to participate in the proximal propulsion of blood toward the heart. Although the proximal propulsion was perhaps not as effective as in normal subjects, it did occur. Some residual contrast material was often found remaining in collateral veins of the thigh. In

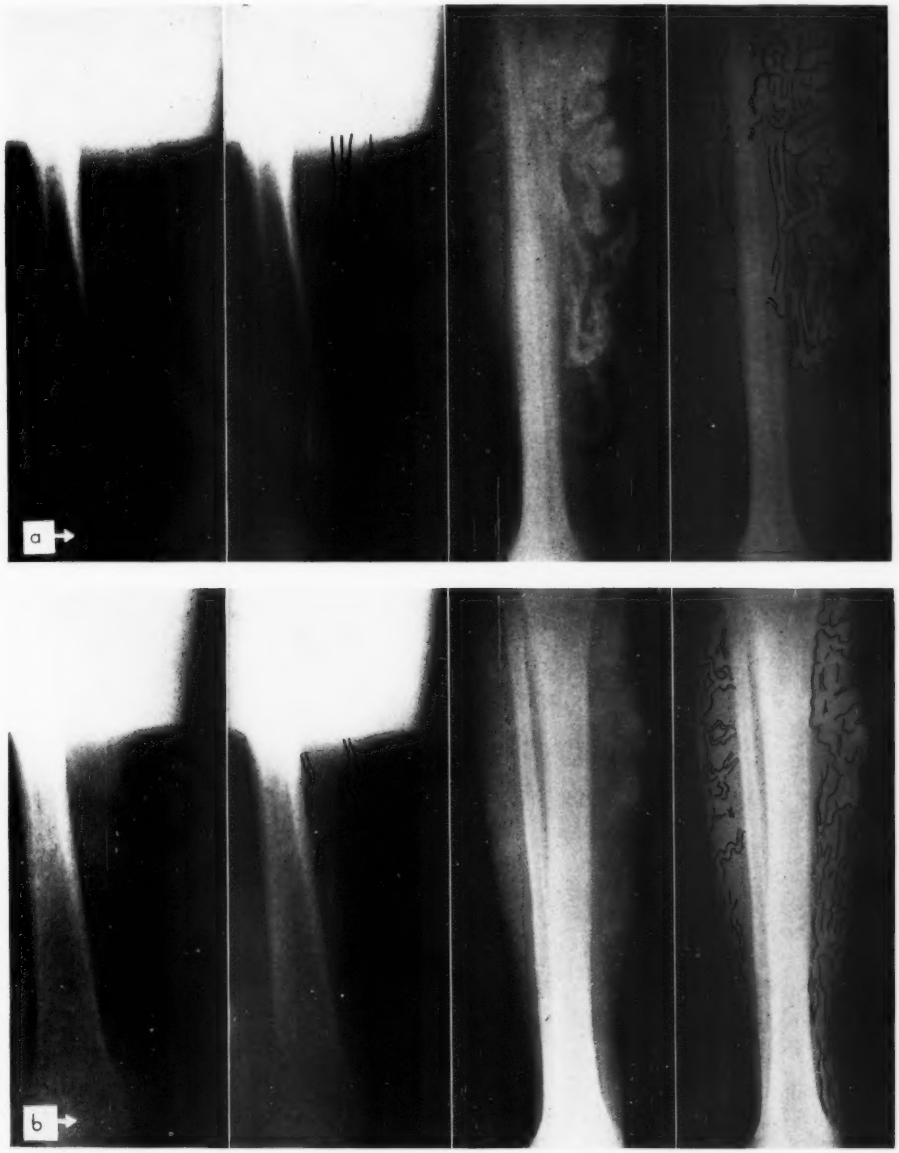

Fig. 5. Functional superficial venography in a patient with varicose veins following injection of radiopaque solution into the saphenous vein, above the knee. The resting dependent films, a, show opacification of the varices, the main saphenous not being opacified above the point of injection. The popliteal and femoral veins are filled. After exercise the contrast material has been cleared from the deep venous circulation, but incompletely from the varicosities, b. Caudal drifting of the opaque material has occurred in the varices. A repeat venographic study on the same limb showed essentially the same findings with the exception that the femoral vein was only faintly opacified in the resting film and more densely opacified after exercise. The second film also showed filling of the major saphenous in the thigh, apparently resulting from regurgitation.

Fig. 6. Functional popliteal venograms in case of mild superficial varicosities. The resting dependent films, a, show excellent visualization of the popliteal and femoral veins with some regurgitation into the varices of the leg and a little regurgitation down the deep veins of the calf. After exercise the material is well cleared from the femoral and popliteal veins with the exception of small amounts at the valve stations. There has been clearing of the deep veins of the calf except for faint filling of their proximal ends. There has been downward drifting of the contrast medium in the varices of the leg although the varices are less well opacified.

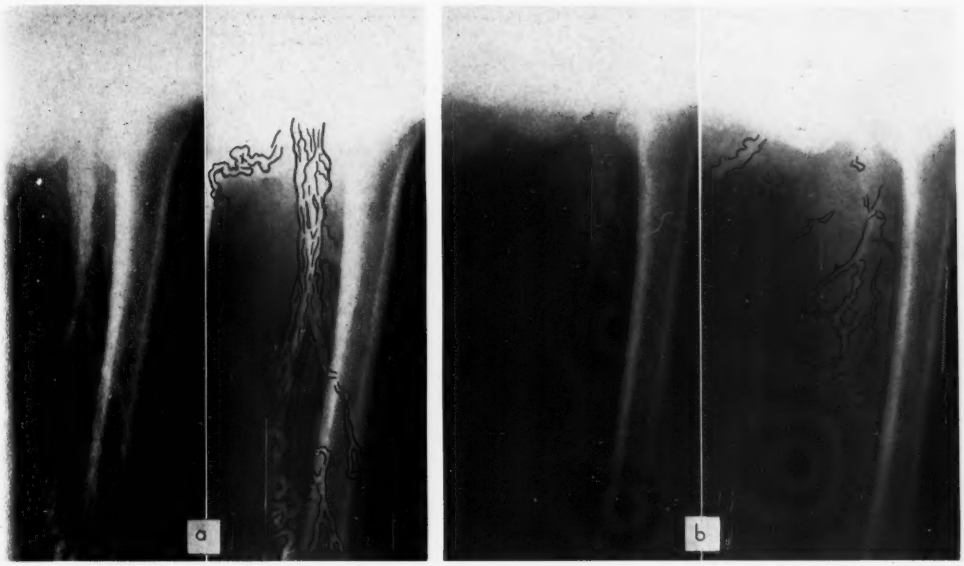

Fig. 7. Functional popliteal venograms in a patient with history of femoroiliac thrombosis and in whom a high and low saphenous ligation had been performed previously. The resting dependent film shows good opacification of distorted, valveless, recanalized femoral and popliteal veins. There was no regurgitation into the veins of the leg. After exercise, there was excellent clearing of the popliteal and femoral veins with faint residual opacification of the collateral vessels of the thigh. No medium was seen in the veins of the leg. On a previous occasion, popliteal venography in the same extremity had been associated with a feeling of faintness and inadequate exercise. These roentgenograms had revealed incomplete emptying of the veins.

In the few instances in which femoral injection was also carried out, it was of interest that no apparent regurgitation down the recanalized femoral vein was observed.

Two symptomatic cases with a history of femoroiliac thrombosis will be presented to illustrate some of these observations. The first patient was a 56 year old woman who had a history of deep thrombophlebitis. She had been troubled with bilateral recurrent leg ulcers. High and low saphenous vein ligations had been carried out and 2 attempts to cover the ulcers with split thickness skin grafts had failed. Injection of the radiopaque material was made into the popliteal vein (Fig. 7). Distorted, valveless, and recanalized femoral and popliteal veins were opacified. They cleared well with exercise. The second patient was a 49 year old man who had had an episode of deep thrombophlebitis following an accident 6 years previously. He had a stasis ulcer for which an unsuccessful attempt at split thickness skin grafting had been carried out. Injection was initially made into the femoral vein in the groin and, a day later, into the popliteal vein (Fig. 8). The first showed regurgitation down some collateral channels but not down the femoral vein. The second showed good opacification of a recanalized femoral vein with a moth-eaten appearance and numerous collateral channels.

In one 52 year old woman a superficial femoral vein ligation and division had been carried out by one of our colleagues 3 years previously because a quiet dependent femoral venogram had revealed regurgitation down the profunda femoral vein. The edema and discomfort of her leg had increased in the 3 years following femoral ligation. Injection was made into a deep vein in the popliteal space (Fig. 9). This study revealed opacification of the profunda femoral vein and a rich collateral circulation between it and the veins in the popliteal area. Excellent clearing occurred

Fig. 8. Functional femoral and popliteal venograms in patient with history of femoroiliac thrombophlebitis. The dependent femoral venograms, a, demonstrate regurgitation down collateral channels but not down the femoral vein. Dependent popliteal venography, b, demonstrates good opacification of a moth-eaten recanalized femoral vein and numerous collateral channels. The postexercise films, not included in this figure, showed good clearing of the femoral vein.

with exercise. In contrast to the cases of superficial femoral venous thrombosis, the ligated superficial femoral vein in this case was not visualized.

Another patient, without a history of deep thrombophlebitis, had a stasis ulcer above the medial malleolus. Functional popliteal venograms showed evidence of a recanalized femoral vein which cleared with exercise. The changes in the femoral vein were presumably due to a previous quiet and unrecognized thrombosis with subsequent recanalization.

Edema of the lower extremity without demonstrable venous pathology. In this small group of patients who complained of edema there was no evidence of venous difficulty, cardiac or renal dysfunction, and, with the exception of 1 patient, no evidence of lymphatic blockade. In all of them, functional venographic studies, principally following popliteal injection, revealed normal veins both anatomically and functionally. In the 1 patient who had clear-cut lymphatic obstruction the studies were carried out merely to demonstrate normal venous pathways in a case of mild elephantiasis. One interesting patient in this group was a 67 year old man who had been crippled by marked bilateral edema of the legs. Though the cause of his edema remains entirely unknown, he has done remarkably well since he began to use proper compression support.

DISCUSSION

The results of this study would indicate that functional evaluation of the veins of the lower extremity by venography necessitates the use of both dependency and exercise. Whether the injection of radiopaque material is made into the femoral vein in the groin, into the popliteal vein, or into one of the superficial veins of the thigh, leg, or foot, the taking of films both before and after exercise helps greatly in functional interpretation. Although valuable information can be gained from all three sites of injection, popliteal in-

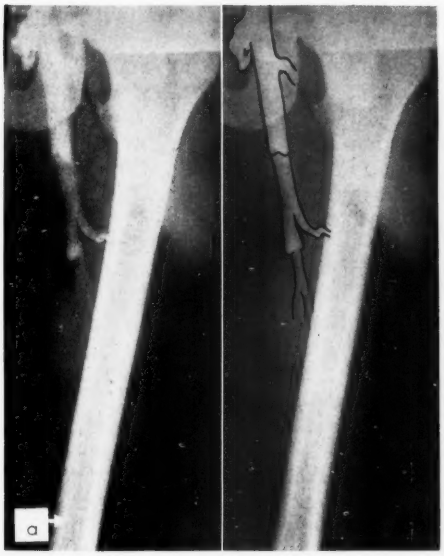

Fig. 9. Femoral retrograde dependent venograms before, and functional popliteal venograms 3 years after, superficial femoral vein ligation and division. The original dependent femoral venograms, a, reveal regurgitation down the profunda femoral vein. The subsequent popliteal venograms, b, demonstrate a rich collateral circulation between the veins in the popliteal space and the profunda femoral system and regurgitation down the veins of the leg. The superficial femoral vein is not opacified. Postexercise films, not included in this illustration, show excellent clearing of the contrast medium from the veins of the thigh and leg.

jection appears to be the most, and femoral injection the least, useful. Popliteal venography not only gives valuable functional information but, in addition, provides such good anatomic delineation of the veins of the lower extremity that there no longer appears to be any real indication for horizontal venography. Although popliteal-femoral vein delineation is not as clear when the injection is made into a superficial vein of the leg or foot as when it is made directly into the popliteal vein, suitable anatomic and functional studies of both the superficial and deep systems can be made using this technique. This is pos-

sible because the bulk of the radiopaque material so injected is returned in the deep circulation.

The type of radiopaque solution employed varied during the course of this investigation, neo-iopax being used in the majority of cases. Diodrast was used occasionally. A small intravenous test dose was always given beforehand. There were no serious reactions to the injected material and no demonstrable vascular disturbances resulting from the venipunctures. Small extravasations of the injected material were occasionally encountered but they were not troublesome. Occasionally the use of neo-iopax was associated with some leg pain, presumably due to transient venospasm, and a sensation of faintness. At times these minor reactions prevented proper exercise before the second film was taken. Recently urokon has been substituted for neo-iopax, and thus far these reactions have not been encountered.

The use of functional venographic studies in patients with lymphatic blockade or "idiopathic" edema was useful principally in excluding venous pathology. When injection was made into superficial varicosities, the contrast material drifted downward and most, if not all of it, was returned proximally in the deep circulation. In the postexercise film, some contrast material remained in the distended varices which were at that time more diffusely but less densely opacified than in the original film.

Several conclusions could be drawn from the experiences with functional femoral and popliteal venography in control patients and patients with venous disorders. During quiet dependency, there was a high incidence of regurgitation of the radiopaque solution down the femoral vein following groin injections and down the deep veins of the leg after popliteal injections. This was true both in the extremities of control subjects and in those with venous disorders. Furthermore, the deep veins of all these patients cleared with exercise. These findings do not permit us to regard regurgitation in the deep venous system in quiet dependency as pathologic or as an indication for operative interruption of the femoral or popliteal vein. In no case was there evidence that the deep vein down which regurgitation occurred did not participate in the normal proximal propulsion of blood toward the heart with exercise. We found nothing to lead us to agree with the assumptions of Bauer (3) or Ferreira, Villamil, and Ciruzzi regarding the existence of "idiopathic" regurgitation of a pathologic nature. It would, accordingly, seem fruitless to employ venography routinely in the hope of finding "idiopathic" regurgitation for which deep venous ligation should be carried out.

In addition, nothing was found in this study to indicate that regurgitation occurs down the recanalized vein; in none did we fail to demonstrate clearing of the radiopaque material with exercise. These observations convince us that, contrary to generally held opinions, the recanalized vein does contribute to the proximal propulsion of blood, though perhaps not as effectively as the normal. There appears to be, therefore, no real indication for ligating it. Since this study was begun, no popliteal vein ligations have been performed and only one femoral vein interruption has been carried out. The one femoral vein ligation was performed early in the study and it is doubtful whether this treatment was wise or contributed to the patient's well being.

Functional venography will undoubtedly be found useful in certain unusual patients with signs or symptoms of venous stasis who present some extraordinary problem. The additional information gained in these unusual cases may be of real value in determining the best therapeutic approach, though the routine use of venography would appear unnecessary in most patients in whom the history and physical examination provide a reasonably clear picture of the nature of the patient's venous disorder and the correct treatment.

It is probable that functional venography will find its maximal usefulness in clinical investigations aimed at contributing further to our knowledge of normal and pathologic venous states and the effect of treatment. It might prove valuable in the study of patients with superficial varicosities before and after treatment. Interesting data might be ob-

tained from repeated studies over the course of many years in patients with deep venous obstruction in order to gain a cleared insight into the progression and natural course of such associated changes as recanalization and the development of collateral circulation and of superficial varicosities. It would also be of interest to study by functional venography those patients with postthrombotic sequelae whose course has been influenced favorably by such proper measures as deep, wide, excision of ulcers with skin grafting and the use of proper elastic or pneumatic support.

SUMMARY

1. The literature pertaining to venography of the lower extremities is reviewed with emphasis on those techniques designed to evaluate venous function.

2. Methods of obtaining functional venography of the lower extremity by percutaneous injection of radiopaque material into the femoral vein in the groin, into the popliteal vein, and into a superficial vein in the thigh, leg, or foot are described. The initial films are exposed immediately after injection with the extremity in quiet dependency and a second exposure is made 1 minute later following exercise. The importance of muscle activity in obtaining more accurate functional evaluation is emphasized.

3. The present study, which does not include a previous large experience with quiet dependent femoral venography in normal and abnormal subjects, is based on observations in 115 separate venographic studies before and after exercise of the dependent limb. They include 23 presumably normal subjects without signs or symptoms of venous disorder. The remaining studies were made in patients with signs and symptoms of venous stasis, unexplained edema, or lymphatic blockade.

4. The results of study of normal subjects and patients with deep venous thrombosis, and "idiopathic" leg edema are discussed.

5. Since regurgitation down the femoral vein following femoral injections and down the deep leg veins following popliteal injections was encountered in a high percentage of both normal and abnormal subjects and since the deep venous system in all of these patients cleared after exercise, we are forced to conclude that regurgitation in the deep venous system in quiet dependency is not pathologic and that it is not an indication for operative interruption of either the femoral or popliteal vein.

6. Furthermore, there was no evidence to suggest that pathologic regurgitation occurs in the recanalized vein. All such veins were cleared of radiopaque material following exercise. Since recanalized veins appear to contribute to the proximal propulsion of blood toward the heart, there seems to be no real indication for ligating them.

7. The indications for functional venographic studies are discussed and the possibilities for their use in future controlled investigations of venous disorders of the lower extremities are mentioned.

8. Although neo-iopax was the radiopaque solution used in the majority of patients, recent experience with urokon suggests that it may prove to be more desirable by providing better delineation of veins and perhaps, through the use of smaller quantities, by reducing the incidence of minor reactions such as transient venospasm and the sensation of faintness.

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THE FATE OF MASSIVE AUTOGENOUS AND HOMOGENOUS BONE GRAFTS INCLUDING ARTICULAR SURFACES

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IT HAS been fairly well established that, although homogenous bone grafts are not incorporated into the host as readily as autogenous bone transfers, small homogenous grafts are revitalized rapidly enough to be clinically acceptable. The recent development of bone banks and the reported successful use of homogenous bone which has been stored at —20 degrees C. stimulated the authors to investigate the fate of massive autogenous, homogenous, and delayed homogenous grafts including articular surfaces. This project was undertaken with the premise that, if it is feasible to store bone in a bone bank and utilize it later in bone grafting procedures, it might be possible to preserve whole joints in like manner and utilize them later in whole joint replacements.

The techniques used in this study together with an account of the clinical and roentgenologic results and a preliminary study of the histologic findings have been reported previously.[1] A detailed analysis has now been made of the histologic material made available by this study and it is the purpose of this report to present these observations.

Dogs were used as experimental animals and the knee joint was selected for study. Three series of animals were used: a series with autogenous grafts (18 dogs), a series with delayed homogenous grafts (19 dogs), and a series with direct homogenous grafts (19 dogs). In the series with autogenous grafts, the left knee joint was removed and replanted in its original site. In the series with delayed homogenous grafts, the knee joint was removed, placed in a deep freeze unit and replaced by a similar homogenous graft which had been stored at —20 degrees C. for a period varying from 1 day to several weeks. In the series with direct homogenous grafts, 2 animals were operated on simultaneously, and the knee joints were transferred from one to the other.

In many respects, the fate of these grafts was similar to the published descriptions of Axhausen, Phemister, and others regarding autogenous and homogenous bone transplantations, but, as certain differences in the healing process of autogenous and homogenous bone grafts are apparently greatly magnified by the massiveness of these grafts, it is felt that a detailed analysis of the histologic fate of the whole joint transplants is of importance.

AUTOGENOUS GRAFTS

The 18 animals in the series with autogenous grafts were sacrificed at intervals varying from 1 day to 2 years. Following autopsy, sections of the graft were made in 2 different planes. Longitudinal sections were made through the articular surface of the femur and tibia and included the distal end of the femur and proximal end of the tibia (Fig. 1). These sections included only the graft and did not extend into the host bone. Transverse sections were made through the tibial and femoral step cuts. These sections included tissues from both host and graft.

Longitudinal section through knee joint. The bone marrow and articular cartilage retained the histologic appearance of normal tissues 24 hours after transplantation but by the end of 2 days there was a slight loss of nuclear stainability of the osteocytes and laking of blood in the capillaries of the marrow; otherwise, the marrow and articular cartilage were normal in appearance. Seven days following transplantation, the nuclei of the osteocytes were pyk-

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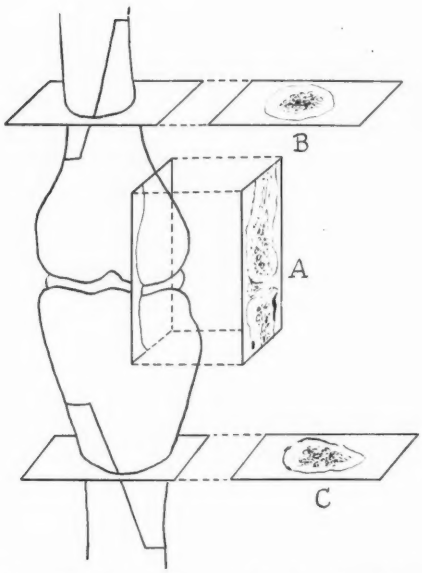


Fig. 1. Drawing to illustrate the planes in which the histologic sections were made. A, Longitudinal section through the weight-bearing area of femur and tibia. B, Transverse section through femoral step cut. C, Transverse section through tibial step cut.

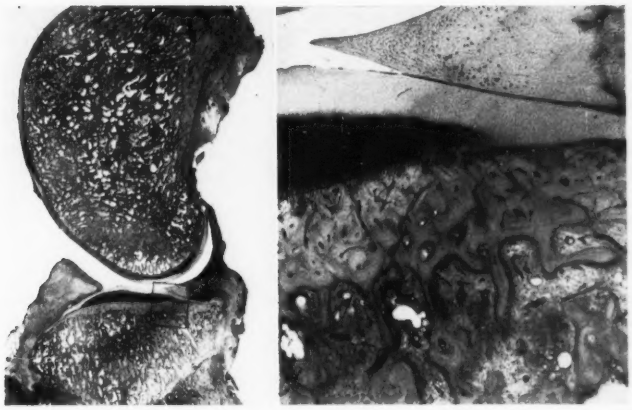
notic throughout. Although cellular outlines were maintained in the marrow, all cells were necrotic. Proximally, in the femoral area, there was evidence of early invasion of the necrotic marrow by a fine-fibered cellular connective tissue. The articular cartilage still retained its normal appearance. Fourteen days following transplantation, there were many empty lacunae in the cortical bone and a few in the spongiosa. The remaining osteocytic nuclei were pyknotic throughout. The old marrow was necrotic but there was rather marked invasion, particularly in the tibial area, by a new fibrous marrow. In association with this new fibrous marrow there was evidence of early resorption of the spongiosa along with early apposition of bone. The articular cartilage still retained its normal appearance except for slight loss of stainability of nuclei of more superficial chondrocytes, especially outside the weight-bearing area.

One month following transplantation, there was much new bone being formed in both the spongiosa and compacta (Fig. 2). The remains of the old bone contained only empty lacunae and there was active resorption of this old bone. Apposition of new bone was taking place simultaneously. The marrow had been completely replaced by a new fibrous marrow which had been transformed into a fatty or myeloid marrow in certain areas. The articular cartilage retained essentially normal appearance except for small local regions of necrosis and reduced stainability of the chondrocytes. The meniscus still retained its normal histologic appearance.

Two months following transplantation, reorganization of the spongiosa was well under way with much new bone being deposited on the old dead trabeculae. The cortical bone revealed much osteoclasis with rapid reorganization in progress. Except for small local regions of necrosis, the marrow was replaced with vital fibrous connective tissue which in many areas had been transformed into myeloid and fatty marrow. The articular cartilage showed local necrosis peripherally with several microscopic osteochondral fractures involving the articular surface and subchondral bone. Early fibrillary degeneration with replacement by fibrocartilage was present in these areas. A fine-fibered connective tissue pannus had appeared, growing in from the periphery. In spite of these changes in the articular cartilage, the meniscus retained normal appearance.

Three months following transplantation, there was continued reorganization of the spongiosa and compacta. More extensive degenerative changes, however, had developed in the articular cartilage which by this time appeared almost entirely necrotic superficially but still appeared viable in the deep layers. Pannus was growing in from the periphery. The subchondral zone, which up to this time had appeared normal histologically, now showed osteocytes with palely stained nuclei but the chondrocytes were of normal appearance. There were a few necrotic fibrocytes in the meniscus, but otherwise it retained its normal appearance.

The specimens 4 months following transplantation revealed that the articular cartilage appeared vital in the deep layer in the weight-bearing area, but elsewhere was either



a b

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Fig. 2. Autogenous knee joint 1 month following transplantation. a, Longitudinal section, ×1.6. b, Field indicated by rectangle in a, ×15.8. c, Transverse section through femoral step cut, ×4.1. Host bone to left and graft to the right.

moribund or necrotic. In local regions there was fibrillary degeneration and fragmentation of the cartilage with invasion by pannus. The meniscus, however, retained essentially normal histologic appearance. All of the osteocytes of the subchondral zone were necrotic but the chondrocytes were of normal appearance. Slow progress in the replacement of the necrotic spongiosa and compacta with new vital bone was apparent.

The most important changes 6 months following transplantation were in the articular surfaces (Fig. 5). Small areas of apparently vital cartilage were still present in the weight-bearing areas, but elsewhere the cartilage was necrotic. There were erosion, fibrillary degeneration, and microscopic osteochondral fractures extending into the subchondral zone. Repair of the cartilage was taking place by pannus which had grown in from the periphery and which was in certain regions being transformed into new fibrocartilage. The chondrocytes of the subchondral zone retained normal appearance, but no osteocytes were seen. The meniscus for the first time showed necrosis and fragmentation peripherally. In certain areas, it was being invaded by scar tissue.

Specimens obtained 9 months following transplantation revealed excellent reorganization of spongiosa and compacta. The spongiosa was entirely replaced by vital new bone except for small local areas where necrotic trabeculae persisted. The cortical bone was

also well reorganized and vital. The marrow was vital throughout with only small areas of fibrous marrow persisting. Elsewhere, it had been converted into normal fatty and myeloid tissue. The articular cartilage, mostly necrotic, was being replaced peripherally by pannus which was being converted into fibrocartilage. The meniscus retained its normal contours, but there were localized regions of necrosis.

Specimens obtained 12, 16, and 17 months following transplantation revealed continued slow reorganization of the spongiosa and compacta (Fig. 8). A few dead tracts were noted in the compacta but generally the bone was well reorganized. Only small areas of vital cartilage remained. These were in the weight-bearing areas and deeply placed. There was extensive fibrillary degeneration and fragmentation of the necrotic cartilage, being repaired by a heavy pannus which was in process of conversion to fibrocartilage. The meniscus showed only minor degenerative changes and retained normal contour.

Two years following transplantation, there was apparently vital hyalin cartilage in the deep layers of the patellar groove and weight-bearing areas of the tibia and femur, but it was covered superficially throughout with dense connective tissue and fibrocartilage (Fig. 11). Similarly, the meniscus was covered to more than half its depth by fibrocartilage. The subchondral zone had a normal appearance with normal chondrocytes and osteocytes. The spongiosa and cortical bone were vital throughout with some active reconstruction still taking place in the compacta. The marrow was vital and yellow except for small local areas of fibrous marrow.

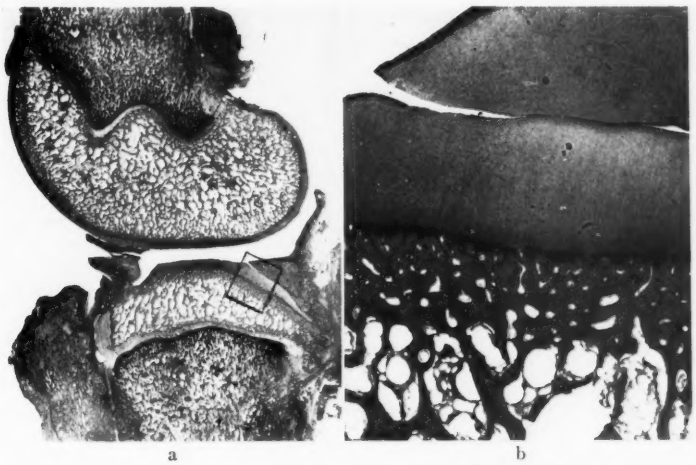
Transverse section—femur and tibia. The bone and marrow in the step cut region of the femur and tibia appeared essentially normal 24 hours after transplantation except for a blood clot about the junction of the host and graft and some extravasated red blood corpuscles in the marrow. There was early cloudy swelling of the contents of the haversian canals with mild pyknosis of endothelial and fibrocytic nuclei. Two days following transplantation, there was slight loss of stainability of the nuclei of most of the osteocytes, and some appeared pyknotic. There were more extensive pyknosis and cloudy swelling in the contents of the haversian canals than had been noted in the 24 hour specimen.

An early internal osteofibrous callus had formed 7 days following transplantation, and in areas partial fibrous union to the host had occurred. There was almost complete necrosis of the contents of the haversian canals in the bone of the graft while the haversian canals in the bone of the host contained vital tissue. The osteocytic nuclei of the graft were pyknotic, but were of normal appearance in the host bone. Fibrous union was present 14 days after transplantation and an osseous callus had appeared on the host side of the junction. It was difficult to distinguish between bone of host and graft, as dead tracts were present in both. There was beginning revascularization of the haversian canals in the subperiosteal area of both the host and graft. More than half of the marrow had been replaced by a vascular, cellular fibrous tissue.

By 1 month there was bony union of the host and graft with the presence of both internal and external callus (Fig. 2). Revascularization of the haversian canals was nearly complete. Rapid reorganization of the cortical bone was under way with only a few dead tracts remaining in the host bone and with much new appositional bone in the graft fragment. Specimens at 2 and 3 months following transplantation revealed rapid progress in reorganization. By 3 months, revascularization was complete and there was enlargement of the haversian canals associated with active apposition of new bone within them. A few dead tracts persisted in both host and graft with a few more in the graft than in the host. Reorganization continued until 9 months, at which time bone of the graft could not be differentiated from that of the host. Both had the histologic appearance of normal bone and the seams could not be identified. Further specimens obtained at 12, 16, 17, and 24 months showed normal bone, haversian canals, and marrow (Figs. 8 and 11).

DIRECT HOMOGENOUS GRAFTS

Nineteen animals with direct homogenous knee joint transplantations were studied.



a b

c

Fig. 3. Direct homogenous knee joint 1 month following transplantation. a, Longitudinal section, ×1.7. b, Field indicated by rectangle in a, ×15.8. c, Transverse section through tibial step cut, ×4.4. Upper half is host, lower half, graft.

These animals were sacrificed at intervals varying from 1 day to 2 years and sections for histologic study were made as noted previously for the series with autogenous grafts.

Longitudinal section through joint. Two days following transplantation, the meniscus, articular cartilage, and cortical bone retained essentially normal histologic appearance. The nuclei of the osteocytes and of the cells of the marrow stained palely but retained their normal shape. Seven days after transplantation, some of the chondrocytic nuclei in the articular cartilage stained palely. The meniscus and subchondral zone retained normal appearance. The nuclei of the osteocytes were pyknotic and the marrow had become necrotic throughout.

Twenty-one days following transplantation, most of the spongiosa and compacta were necrotic, as manifested by empty lacunae. There was lessened stainability of the articular cartilage, but it retained normal contour. The meniscus was covered with a fine-fibered connective tissue and its nuclei had lost most of their stainability. New fibrous marrow was invading the necrotic marrow from the periphery and new bone formation was taking place in these areas. Similar changes were noted in specimens obtained 1 month following transplantation but, at that time, it was

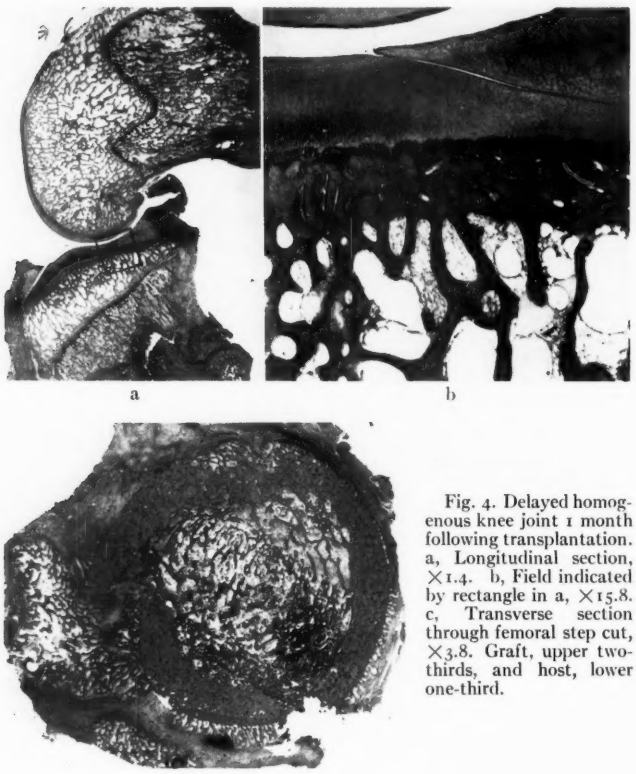


Fig. 4. Delayed homogenous knee joint 1 month following transplantation. a, Longitudinal section, ×1.4. b, Field indicated by rectangle in a, ×15.8. c, Transverse section through femoral step cut, ×3.8. Graft, upper two-thirds, and host, lower one-third.

also noticed that new connective tissue had appeared and was growing in from the periphery over the articular surfaces in the form of a pannus and also over both the superior and inferior surfaces of the meniscus (Fig. 3). The spongiosa and cortical bone were entirely necrotic except for a few regions of early replacement subperiosteally. New fibrous marrow was growing in from the marrow of the shaft as well as from the periosteum.

Six weeks following transplantation, the marginal half of the meniscus was necrotic and the surface was disintegrating. The articular cartilage appeared vital deeply in the weight-bearing area, but was necrotic superficially and peripherally, and fibrillary degeneration had appeared. The spongiosa and cortical bone were necrotic with no more new bone than had been noted at 4 weeks. The marrow was partially replaced by new fibrous tissue. In the subchondral zone it was noted that the osteocytes were necrotic but that the chondrocytes still appeared vital. Essentially the same changes were noted in specimens obtained 2 months following transplantation. At that time, pannus covered much of the articular surface and most of the surface of the meniscus. There were local areas of osteoclasis and osteogenesis involving the subperiosteal areas of the cortical bone.

Three months following transplantation, there was still very little reorganization of the spongiosa or compacta and there had been further degenerative changes in the articular surface. The articular cartilage was fragmented and degenerated and there was thick pannus growing in from the periphery. Multiple osteochondral compression fractures were

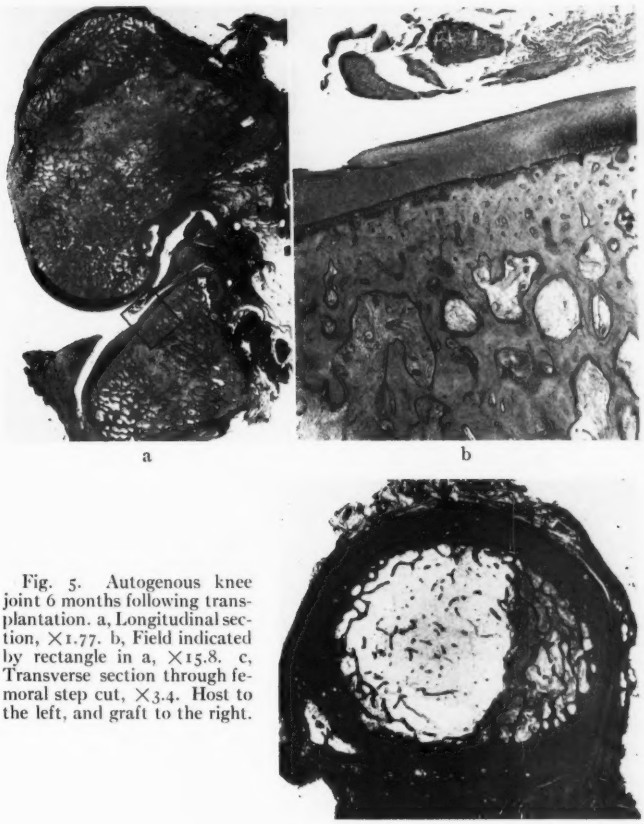


Fig. 5. Autogenous knee joint 6 months following transplantation. a, Longitudinal section, ×1.77. b, Field indicated by rectangle in a, ×15.8. c, Transverse section through femoral step cut, ×3.4. Host to the left, and graft to the right.

present extending into the subchondral zone. The specimens obtained 4 months following transplantation revealed similar findings with evidence of replacement of the necrotic meniscus by thick pannus. The articular cartilage was badly eroded, showed fibrillary degeneration and multiple compression fractures, but there were still a few deeply situated areas of hyalin cartilage which appeared vital. The marrow had been replaced almost completely by vital fine-fibered connective tissue. There was evidence of early reorganization of the necrotic spongiosa and compacta but this had not progressed greatly beyond that seen in the specimen 3 months following transplantation. The specimens obtained at 6 months revealed a picture almost identical with that seen at 4 months (Fig. 6). There was very little evidence of reorganization of the spongiosa which was entirely necrotic. Most of the cortical bone was still necrotic, but there was active new bone formation subperiosteally. Eight months following transplantation, there was possibly a little more evidence of repair of the degenerated and eroded articular surface with ingrowth of pannus, but generally, there had been very little progress in reorganization or replacement, the picture remaining about the same as noted at 4 and 6 months.

Further degenerative changes were apparent 12 months following transplantation (Fig. 9). The meniscus was not recognizable, only necrotic debris being present in the joint cavity. The articular cartilage was completely

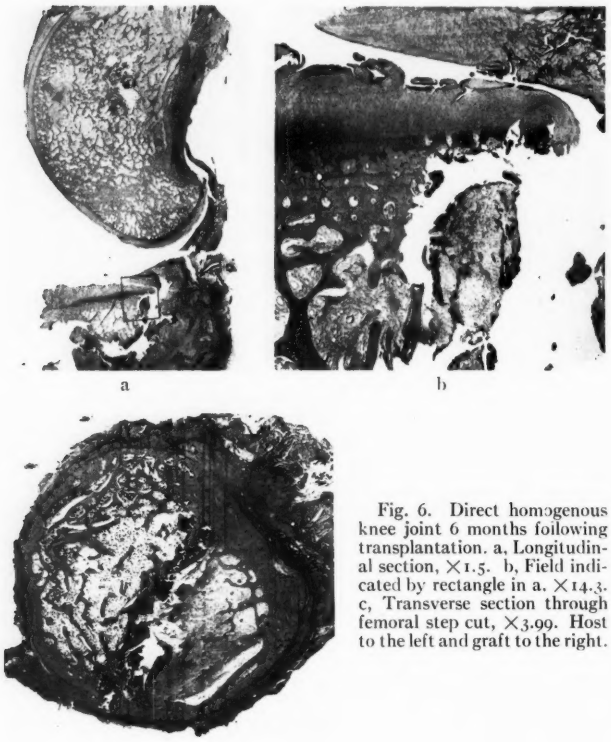


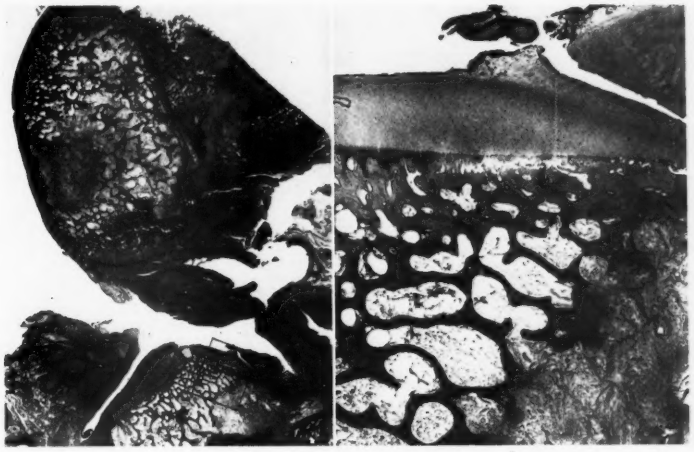
Fig. 6. Direct homogenous knee joint 6 months following transplantation. a, Longitudinal section, ×1.5. b, Field indicated by rectangle in a. ×14.3. c, Transverse section through femoral step cut, ×3.99. Host to the left and graft to the right.

lost in the weight-bearing area and was replaced by a thick scar tissue. Elsewhere, the cartilage was necrotic and degenerating. The subchondral zone showed a few vital chondrocytes, but otherwise was necrotic. The spongiosa was necrotic and showed very little evidence of replacement. Active reorganization of the compacta was taking place, but most of the cortical bone remained necrotic. The marrow was mostly vital fibrous tissue grading into scar tissue in some regions.

Specimens obtained 16 months following transplantion revealed a picture essentially unchanged from that noted at 12 months. There was very little progress in reorganization or repair.

Two years following transplantation, there was evidence of progressive but slow repair (Fig. 12). The meniscus had been replaced by fibrocartilage and the articular surface was covered largely with new fibrocartilage. There still remained local areas of necrotic hyalin cartilage which showed erosion and fibrillary degeneration. The subchondral zone contained many vital chondrocytes but there were no osteocytes. Much of the spongiosa toward the shaft had been replaced by new vital bone but there were large regions of necrotic spongiosa beneath the weight-bearing areas of tibia and femur. The cortical bone was fairly well reorganized, but many dead tracts were still present. The marrow was either yellow or myeloid in those areas where the spongiosa was vital, but fibrous in those areas where the spongiosa was necrotic.

Transverse section—femur and tibia. Two days after transplantation, the marrow appeared vital but there were pyknotic changes in the nuclei of the osteocytes and cloudy swelling in the tissues of the haversian canals.



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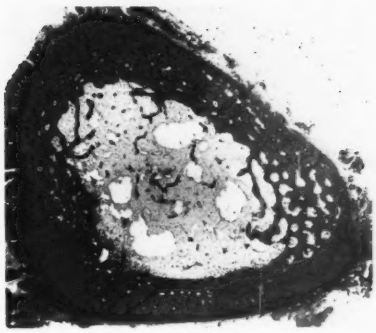

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Fig. 7. Delayed homogenous knee joint 6 months following transplantation. a, Longitudinal section, ×2.2. b, Field indicated by rectangle in a, ×15.8. Note invading new fibrous marrow lower right. c, Transverse section through tibial step cut, ×4.0.

Seven days following transplantation, there was fibrous union of the host and graft and new bone formation at all of the seams. There was evidence of avascular necrosis of the bone of the host as well as that of the graft. A few vital osteocytes were still present but most appeared moribund with pyknotic or palely staining nuclei. The contents of the haversian canals were moribund or necrotic, but there was evidence of revascularization beginning in the subperiosteal areas. The marrow of the graft was necrotic throughout. After 14 days, there was partial bony union with an organizing fibro-osseous callus at the seams. Empty lacunae were present in the cortical bone of both the host and graft. New cellular fibrous tissue was invading the necrotic marrow. Twenty-one days following transplantation, the bone of the host was largely vital with only a few dead tracts while the bone of the graft was almost entirely necrotic. There was early revascularization of the haversian canals and there was much new bone formation at the seams. The marrow had been almost completely replaced.

Specimens obtained at 1 month, 6 weeks, 2 months, and 3 months reveal progressive revascularization of the bone of both the graft and host with completion of this process by the end of 3 months. Bony union of the host and graft was present by 1 month although most of the graft was necrotic at that time and there were many dead tracts in the host bone (Fig. 3). There was evidence of osteo-

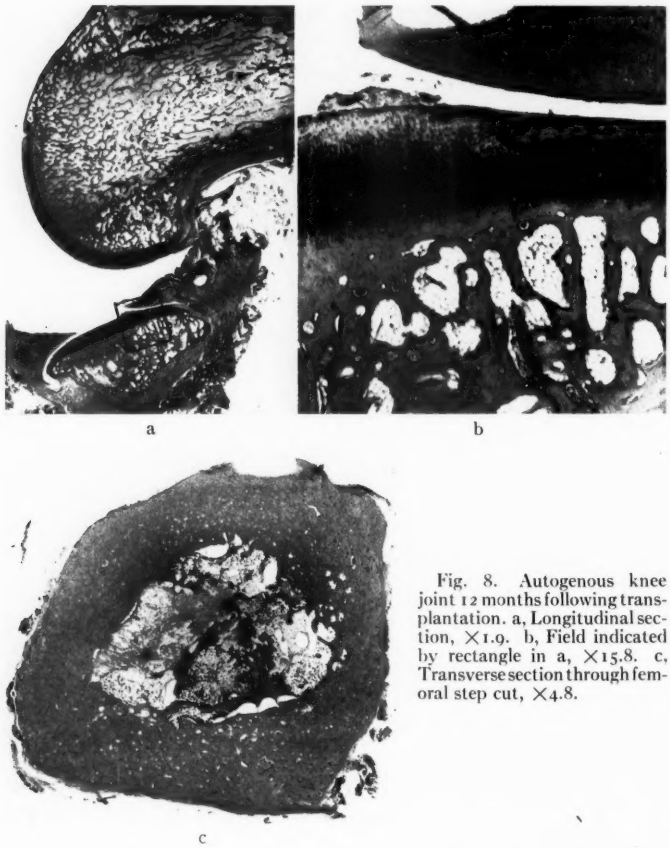


Fig. 8. Autogenous knee joint 12 months following transplantation. a, Longitudinal section, ×1.9. b, Field indicated by rectangle in a, ×15.8. c, Transverse section through femoral step cut, ×4.8.

clasis and osteogenesis in all of the specimens. In the 3 month specimen, the host bone was mostly vital with only a few dead tracts, but the graft was still largely necrotic with empty lacunae, although it was completely revascularized. Specimens obtained at 4, 6, and 8 months after transplantation revealed steady progress in reorganization of the osseous callus forming the union at the seams (Fig. 6).

At 8 months, it was difficult to identify the seams. Complete revascularization was present in both host and graft in all of these specimens. Generally, host bone was vital although a few dead tracts persisted. There was evidence of reorganization in the subperiosteal region of the graft, but the graft in both the femoral and tibial step cut areas remained largely necrotic. In the specimen obtained 1 year following transplantation, the graft in the femoral step cut area was entirely necrotic and most of the tibial graft was necrotic (Fig. 9). In spite of this, there remained excellent bony union. Similar findings were present in the specimen obtained 16 months following transplantation. In the specimen obtained 2 years following transplantation, however, reorganization had progressed so that it was difficult to differentiate between host and graft, the graft having been replaced by new vital bone (Fig. 12).

DELAYED HOMOGENOUS GRAFTS

Nineteen animals with delayed homogenous knee joint transplantations were sacrificed at

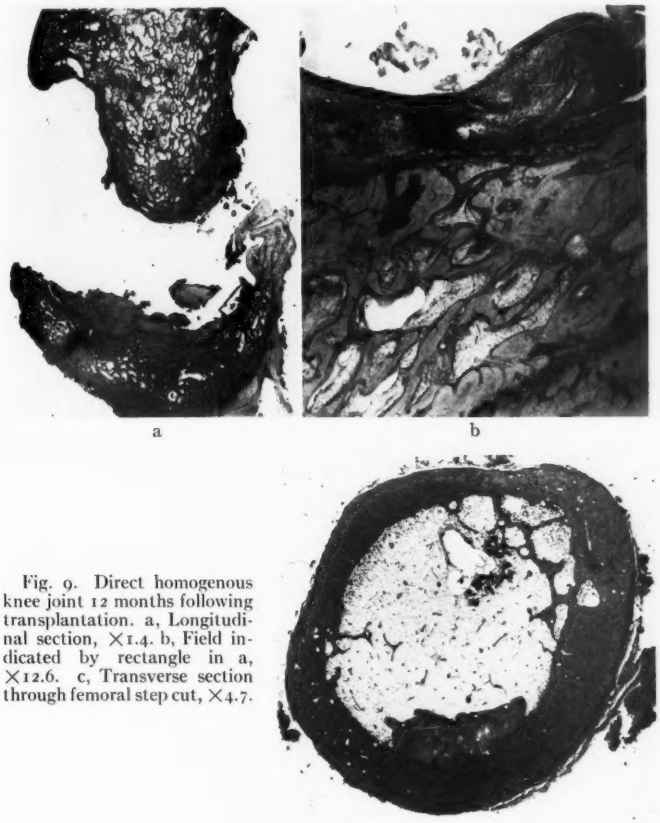


Fig. 9. Direct homogenous knee joint 12 months following transplantation. a, Longitudinal section, ×1.4. b, Field indicated by rectangle in a, ×12.6. c, Transverse section through femoral step cut, ×4.7.

intervals varying from 1 day to 2 years and the histologic changes in the grafts studied. Sections were made as indicated previously in the series with autogenous grafts.

Longitudinal section through joint. The specimen obtained 24 hours following transplantation revealed that there were early necrotic changes in the marrow. The osteocytes in the cortical bone appeared moribund and the nuclei of the osteocytes of the spongiosa stained palely. The subchondral zone, however, retained a normal histologic appearance. Seven days following transplantation, the distal third of the meniscus was moribund or necrotic. The weight-bearing area of the articular cartilage retained a normal histologic appearance, but elsewhere, it was palely stained and there was superficial necrosis. The marrow was necrotic throughout and the osteocytes in the spongiosa and compacta were either moribund or necrotic. Fourteen days after transplantation, the weight-bearing area of the articular cartilage still appeared vital. The remainder of the articular surface, the spongiosa, the compacta, and the marrow were all necrotic. One month following transplantation, there was extensive pannus formation peripherally over the necrotic articular cartilage and also over the necrotic meniscus (Fig. 4). A small amount of apparently vital hyalin cartilage was still present in the deep half of the weight-bearing area. The chondrocytes in the subchondral zone appeared vital but the osteocytes were ne-

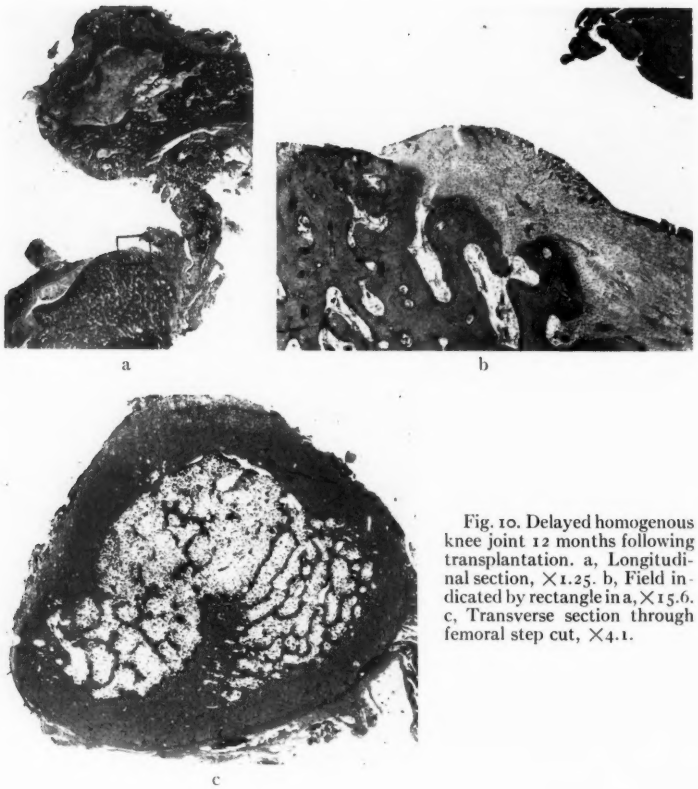
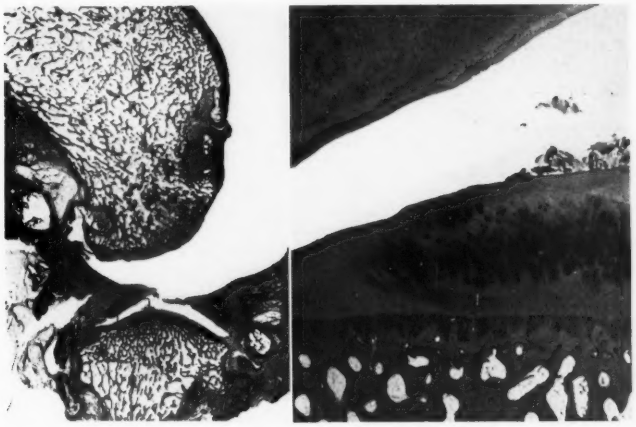


Fig. 10. Delayed homogenous knee joint 12 months following transplantation. a, Longitudinal section, ×1.25. b, Field indicated by rectangle in a, ×15.6. c, Transverse section through femoral step cut, ×4.1.

crotic. The necrotic marrow was being invaded by new cellular connective tissue and there was evidence of early replacement in the compacta.

There were still apparently viable chondrocytes in the deep layers of the weight-bearing area of the articular cartilage 2 months following transplantation, but otherwise the articular cartilage was necrotic and was covered over most of its surface with a fine-fibered connective tissue pannus. The meniscus was being replaced by a fine-fibered connective tissue peripherally and had degenerated marginally. The marrow had been largely replaced, but there was no evidence of new bone formation upon the trabeculae of the necrotic spongiosa. There was considerable osteoclasis subperiosteally but very little new bone formation on the old cortical bone. Specimens obtained 3 months following transplantation revealed fibrillary degeneration of the articular surface, and early erosion. A few stainable chondrocytes were still present, but otherwise, the subchondral zone as well as the articular cartilage was completely necrotic. Although the marrow was completely replaced by vital fibrous tissue, there was no evidence of replacement of the necrotic spongiosa and very little replacement of the compacta. The specimens obtained at 4 and 6 months revealed a similar picture with further fragmentation and erosion of the articular surface (Fig. 7). There was very little replacement of the compacta and none of the spongiosa.

One year following transplantation, practically all of the hyalin cartilage had disappeared and the articular surface was covered



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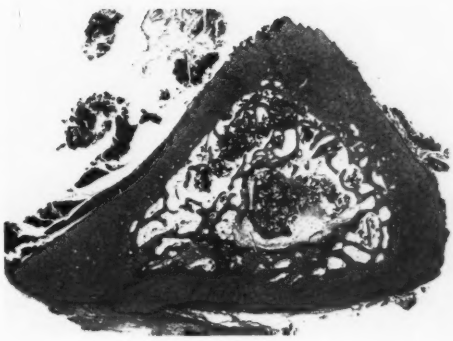

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Fig. 11. Autogenous knee joint 24 months following transplantation. a, Longitudinal section, ×1.7. b, Field indicated by rectangle in a, ×15.8. c, Transverse section through tibial step cut, ×4.1.

with pannus or new fibrocartilage (Fig. 10). The spongiosa was partially replaced by compact bone and there was irregular replacement of the cortical bone. After 16 months, the articular surface was covered with pannus which in some areas was transformed into heavy scar tissue, in others into fibrocartilage. The spongiosa was still largely necrotic with local areas of active resorption. The cortical bone was fairly well reorganized but there was still a large amount of necrotic compacta present.

In the specimen obtained 2 years following transplantation, the articular surface showed fibrillary degeneration, fragmentation, and microscopic osteochondral fractures locally (Fig. 13). Repair was still in progress as evidenced by pannus overgrowth, scar tissue formation, and new fibrocartilage. The meniscus was composed peripherally of fibrocartilage and was badly frayed and fragmented in the marginal half. The spongiosa was still largely necrotic with only slight replacement in a few regions. The cortical bone was largely replaced, although a number of dead tracts were still present, and the haversian canals were considerably widened. The marrow was vital throughout, mostly fibrous, with local areas of yellow marrow.

Transverse section—femur and tibia. Twenty-four hours following transplantation, the host bone was essentially normal in appearance, but the osteocytes in the graft were pyknotic and the haversian canals contained fibrin clot. There was extravasation of red blood corpuscles in the marrow and there was

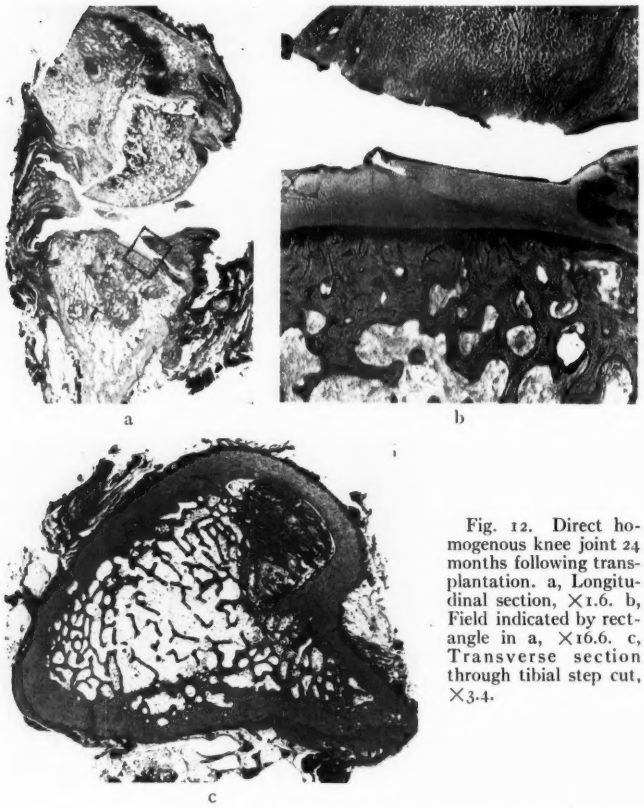
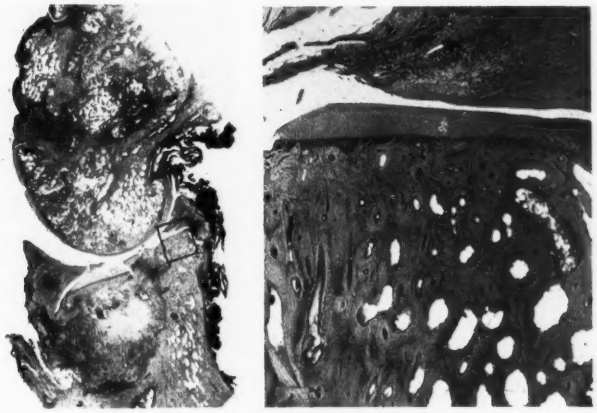


Fig. 12. Direct homogenous knee joint 24 months following transplantation. a, Longitudinal section, ×1.6. b, Field indicated by rectangle in a, ×16.6. c, Transverse section through tibial step cut, ×3.4.

pyknosis of most of its nuclei. After 7 days, the bone of the graft was necrotic and a few dead tracts were seen in the cortical bone of the host. The haversian canals of the graft contained only necrotic tissue. The marrow was dead in the graft and vital in the host. By 14 days, there was fibrous union at the junction of graft and host with considerable osseous callus on the host side, but none on the graft side. There was evidence of some revascularization of the haversian canals of the host but no repair in the graft. The bone of the host was vital while that of the graft was dead.

By 1 month following transplantation, the marrow was vital throughout and revascularization of the graft was far advanced, the revascularization occurring both from the new vascular tissue which had invaded the necrotic marrow and by invasion of the haversian canals by vessels from the periosteum (Fig. 4). The graft was joined to the host bone firmly by an osteochondral callus. The bone of the host retained essentially normal histologic appearance; that of the graft was entirely necrotic. By 2 months, there was excellent bony union. At the junction of the graft with the host, there was beginning reorganization of the callus. The graft was almost completely revascularized. A little new subperiosteal bone had formed on the graft but, whereas most of the bone of the graft remained necrotic, only an occasional dead tract was found in that of the host. By 3 months, the callus at the junction of the graft to host was well reorganized, with firm bony union. Revascularization of the graft was almost complete and the haversian canals were widened. Active osteoclasis was present



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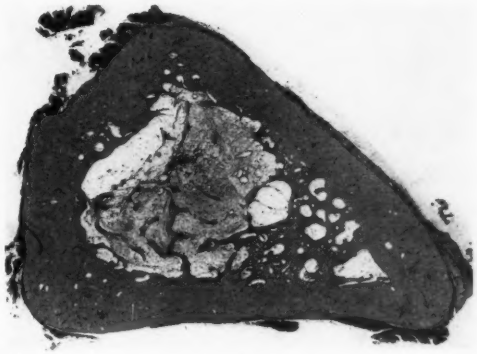

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Fig. 13. Delayed homogenous knee joint 24 months following transplantation. a, Longitudinal section, ×1.7. b, Field indicated by rectangle in a, ×15.4. c, Transverse section through tibial step cut, ×4.4.

and there was evidence of new bone formation. Most of the graft, however, remained necrotic. By 4 months, the seams between graft and host could be identified only with difficulty. Revascularization was complete, with enlargement of the haversian canals, and active replacement of the necrotic graft was under way. One specimen obtained at 6 months revealed excellent reorganization of the graft which had been almost completely replaced by vital bone except for regional dead tracts (Fig. 7). In specimens obtained at 12 and 16 months, however, it was found that, although there was excellent bony union and the seams between graft and host could not be definitely identified and although revascularization was complete, the graft bone remained largely necrotic while that of the host was vital (Fig. 10). In all, there was evidence of slow but active replacement of the necrotic bone through osteoclasis and osteogenesis occurring subperiosteally. Even after 2 years, the picture was much the same with the bone of the graft remaining largely necrotic and with only partial replacement by endosteal and periosteal new bone formation. This was in spite of complete revascularization of bone and marrow which had essentially normal histologic appearance (Fig. 13).

COMPARATIVE ANALYSIS OF THE FATE OF VARIOUS COMPONENTS OF AUTOGENOUS, DELAYED, AND DIRECT HOMOGENOUS KNEE JOINT TRANSPLANTATIONS

After the fate of the whole joint transplants over a 2 year period had been studied in each

of the three series, a comparative study of the various elements of the transplant was made. This has revealed important differences in the timing of the healing process.

Meniscus. In some specimens in the series with autogenous transplantations, the meniscus retained essentially normal appearance both grossly and microscopically for periods up to 3 to 4 months following operation and, in 1 specimen at 9 months and 1 at 12 months, the meniscus still had a normal appearance. In others, local necrotic changes appeared as early as 3 months. Repair took place through the invasion and pannus-like overgrowth of relatively fine-fibered connective tissue which, in part, became fibrocartilaginous. This repair was progressive and well advanced by 16 to 24 months. The morphology was fairly well preserved throughout the series.

In the series with direct homogenous transplantations, necrotic changes characterized by palely staining nuclei of chondrocytes were present as early as 14 days. Progressive necrosis then occurred with fragmentation and loss of part or all of the marginal half of the meniscus as early as 2 months following transplantation. Replacement of the necrotic fibrocartilage by fine-fibered connective tissue proceeded somewhat irregularly. In some specimens the meniscus was completely destroyed and fragmented; in others the meniscus was entirely replaced by new fibrocartilage which showed minor superficial erosions.

In the series with delayed homogenous transfers, the meniscus was necrotic as early as 7 days and new connective tissue pannus appeared as early as 30 days. Irregular replacement by new connective tissue and fibrocartilage followed. The marginal half of the meniscus became fragmented and lost. In specimens obtained at 12 and 16 months, the entire meniscus was degenerated with only ineffective repair taking place in the base of the meniscus. In the 2 year specimen, the peripheral portion of the meniscus was replaced by new fibrocartilage while the marginal half was badly fragmented.

Articular cartilage. In the series with autogenous transplantations, the articular cartilage retained an essentially normal histologic appearance up to 14 days and then early necrotic changes appeared regionally, manifested by faint stainability of chondrocytes and matrix. This was progressive, beginning superficially, the deep layers retaining viability longer. The superficial half was largely necrotic by 3 months with the deeper half showing only local necrosis by 4 months. It was also noticed that the cartilage in the weight-bearing area retained viability longer than in the peripheral regions. Repair in the form of early pannus formation was present by 2 months. The pannus progressed centrally and replaced the necrotic cartilage by either scar tissue or fibrocartilage. Microscopic osteochondral fractures were common and these healed by formation of either scar tissue or fibrocartilage. In the 2 year specimen, there were still small areas of necrosis in the weight-bearing area but the articular surface was covered with either a dense fibrous tissue or fibrocartilage.

In the series with direct homogenous transplantations, there was evidence of regional necrosis manifested by palely staining chondrocytes and matrix as early as 7 days. Necrosis appeared earlier and progressed more rapidly than in the autogenous grafts. It was much more extensive, but a few of the deep cells remained apparently viable up to 8 months. Eventually, however, all cells became necrotic or degenerated. There was marked fibrillary degeneration and erosion which became apparent at 5 weeks; and by 12 months, most of the cartilage had disappeared. Pannus formation was present by 30 days, but progressed much more slowly and was not as effective as in the autogenous grafts. Fibrocartilage replacement was only slight up through the 24 month specimen.

The articular cartilage of the delayed homogenous transplants followed a time schedule almost identical with that of the direct homogenous grafts. Regional necrosis was present by 7 days, but some of the deeper cells remained viable up to 3 months. Thereafter, the entire articular cartilage appeared necrotic. Repair was by pannus overgrowth which appeared as early as 30 days, but progressed slowly and ineffectively. There was severe fibrillary degeneration and erosion with many microscopic osteochondral fractures.

Replacement was largely by scar tissue but in specimens obtained in from 1 to 2 years, there were areas of transformation into fibrocartilage.

Spongiosa. The osteocytic nuclei of the spongiosa in the autogenous grafts showed slight loss of stainability by 2 days, pyknosis by 7 days, and the lacunae were mostly empty by 14 days. In the massive portion of the graft, the spongiosa apparently all became necrotic.

Replacement involving apposition of new bone upon and resorption of the old necrotic trabeculae appeared as early as 14 days, and progressed rapidly. Reorganization was largely complete by 9 months.

In the direct homogenous grafts, the nuclei of the osteocytes appeared palely staining by 2 days, pyknotic by 7 days and the lacunae were empty by 14 days, as was noted in the autogenous series. Replacement, however, took place only sporadically with most of the spongiosa remaining necrotic up to 16 months. Even at 24 months, a large amount of necrotic spongiosa persisted although some apposition of bone was present.

Similar changes were noted in the delayed homogenous grafts, but there was even less attempt at repair. Except for slight osteoclasis in a 3 month specimen, active osteogenesis in the subchondral area of a 12 month specimen, and slight apposition of new bone in the 24 month specimen, there was no attempt at repair.

Cortical bone. As in the spongiosa, the nuclei of osteocytes of the cortical bone in all 3 types of grafts showed poor stainability by 2 days, pyknosis by 7 days, and most of the lacunae were empty by 14 days. Reorganization by concomitant osteoclasis and osteogenesis was present in all 3 series by 30 days. This replacement proceeded uniformly in the autogenous grafts until almost complete reorganization was present by 9 months. Although the reorganization started at about the same time as in the autogenous grafts, it proceeded at a much slower rate in both the delayed and the direct homogenous transfers. Not until after 2 years was the bone fairly well reorganized and even then there were many dead tracts.

Marrow. The marrow of the autogenous grafts appeared normal up to 2 days following which rapid necrosis occurred until all appeared necrotic by 7 days. At this time there was early invasion by a new cellular connective tissue from the cambium layer of the periosteum and the marrow of the host. This invasion progressed rapidly to a state of nearly complete replacement by the end of 30 days, at which time there was some transition into myeloid and fatty marrow. This transition was almost complete by the end of 9 months.

In the direct homogenous grafts, the marrow was palely stained by the end of 2 days and completely necrotic by 7 days. Early invasion by new cellular connective tissue was apparent in the 14 day specimen but there was no evidence of transition into yellow or red marrow.

The marrow of the delayed homogenous grafts behaved very much as noted in the direct homogenous transfers but was completely necrotic at the end of 2 days. Although there was new invading connective tissue at 14 days, small areas of necrosis persisted, particularly under the weight-bearing areas, up to 16 months. There was no evidence of transition into yellow or red marrow up to 2 years and even in the 2 year specimens, there were only regional areas of yellow marrow. No myeloid marrow was noted in any of the delayed homogenous transplants.

Union of the step cut. Very little difference in the timing or character of the union of host and graft at the step cut area was noted in the 3 different types of grafts. In all, fibro-osseous callus was present by 7 days and bony union was found to be present by 30 days. This union was quite mature and remained firm throughout all three series.

Contents of haversian canals. In the autogenous grafts, the contents of the haversian canals showed early necrotic changes by 2 days. Most of the haversian canals were either empty or contained necrotic tissue after 7 days. There was, however, evidence of early revascularization by 2 weeks and almost complete revascularization by the end of 30 days. In both the direct and delayed homogenous grafts, very similar changes were noted

with complete necrosis of the contents of the haversian canal being present by 7 days, early revascularization apparent at 14 days and most of the canals revascularized by 30 days.

Cortical bone of step cut area. A few of the tracts in the cortical bone of the step cut area remained viable in the autogenous grafts. Most, however, showed loss of nuclear stainability by 2 days and necrosis by 7 days. Reorganization by concomitant osteoclasis and osteogenesis was well under way by 30 days and was complete by 9 months. In most instances the tibia showed more rapid reorganization than the femur.

In the direct homogenous grafts, progressive necrotic changes were present at from 2 days to 1 month at which latter time practically all of the lacunae were empty. Reorganization did not appear until 6 weeks and then progressed very irregularly, although as already noted, bony union was present in all specimens by 30 days. Many dead tracts appeared in all of the specimens up until 2 years at which time the cortical bone was found to be entirely vital.

The osteocytic nuclei of the cortical bone in the step cut area of the delayed homogenous grafts were pyknotic at the end of 24 hours and the bone was entirely necrotic by 14 days. Early attempts at reorganization were noted at 30 days but repair was sporadic with many dead tracts remaining up to and including the 2 year specimen. It is to be noted in this series that in spite of the slow and irregular reorganization of the cortical bone, bony union at the junction of graft and host was present at 30 days.

SUMMARY

1. The fate of autogenous, delayed homogenous, and direct homogenous knee joint transplantations has been described.

2. The meniscus and articular cartilage behave similarly in delayed homogenous and direct homogenous transplantations, but necrosis appears much earlier in the homogenous grafts than in the autogenous transfers, and repair is much slower and less effective.

3. The spongiosa became necrotic in all three types of grafts, but orderly repair took place in the autogenous transplants with reorganization largely complete by 9 months. In the direct and delayed homogenous grafts, only sporadic attempts at repair were present, with most of the spongiosa remaining necrotic even at 24 months.

4. The cortical bone became necrotic in all three types of grafts and repair began in all at about 30 days. In the autogenous grafts, the reorganization progressed rapidly until it was complete at 9 months while, in both the direct and delayed homogenous grafts, repair was much slower with many dead tracts remaining even at 2 years.

5. The marrow of the autogenous grafts was replaced rapidly by invading connective tissue which was transformed into normal yellow or red marrow by 9 months. Although the necrotic marrow in the direct and delayed homogenous grafts was replaced by invading cellular connective tissue, it was not transformed into yellow or red marrow except in small, scattered areas even at 2 years.

6. Bony union in the step cut areas occurred as rapidly in the delayed and direct homogenous grafts as in the autogenous.

7. Revascularization of the haversian canals proceeded rapidly in all three types of grafts with the process being almost complete by the end of 30 days.

8. In the autogenous grafts, a few tracts in the cortical bone in the step cut area remained viable but most of the bone became necrotic. Reorganization appeared by 30 days and progressed orderly until complete at 9 months. In both the direct and delayed homogenous grafts, all osteocytes became necrotic; and, although osteoclasis and osteogenesis were present by 30 days, repair was not complete until 2 years in the direct homogenous graft, and there were still a few dead tracts even at 2 years in the delayed homogenous graft.

CHRONIC ULCER OF THE LEG IN YOUNG SUBJECTS

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THE chronic ulcer of the leg is a perennially recurring subject for discussion in the medical journals of both Great Britain and America. Temporarily eclipsed by matters of seemingly greater import, it is periodically lifted into prominence again by the exposition of some new line of treatment or by the re-emphasizing of some particular theory of causation. The ulcer discussed in most of the contributions to the literature is that which has been known until recently as the "varicose" ulcer, and which is seen in its most classic form in the elderly frequenter—usually a woman—of the surgical outpatient or the dermatologic clinic. Perhaps one reason for the failure of the profession to find a cure for this complaint has been the fact that the patient was so often elderly and uncomplaining and had learned to live with her ulcer without too much inconvenience or loss of earning power.

Now, however, the problem is presenting itself in a new and much more urgent light. Several years of practice in the hospitals of the Ministry of Pensions have brought this new development very strongly home to me. My patients with ulceration of the leg are young and healthy men with their lives and fortunes still before them. Acute, severe, and crippling pain, prolonged and often repeated visits to hospital, and sometimes permanent disability and loss of earning power, are the features of the leg ulcers seen today with disconcerting frequency in young men who have returned from service in World War II, and particularly in those who were prisoners of war in the Far Eastern theater.

Admissions to the General Surgical Unit at Queen Mary's Hospital, Roehampton, from May 1950 until December 1952 for chronic ulcer of the leg have numbered 149, representing 115 patients. Of this number, no fewer than 80 patients (69 per cent) were under 50 years of age, and 51 (45 per cent) were under 40. This is a proportion of young subjects which contrasts greatly with the classic ulcer of the ordinary surgical outpatient department. The figures exclude the patients admitted to the orthopedic department with ulcers due to chronic osteomyelitis and gunshot wounds, and also those with ulcerating burn scars who go direct to the care of the plastic surgeons.

Among the miscellaneous clinical material which these figures represent are a few specific conditions, readily recognizable on routine examination and, for the most part, readily amenable to the correct line of treatment. One such group comprises patients with ulceration at the site of an old injury, either a wound or a "tropical" ulcer. The only abnormality is that of a thin and adherent scar, and adequate skin replacement produces rapid and permanent cure. Another smaller group shows the symptoms of obliterative arterial disease and responds satisfactorily to the treatment appropriate to that condition. One patient whom I saw with ulceration of several years' standing had an arteriovenous fistula in the popliteal space which had been overlooked on several hospital admissions and even through an operation for varicose veins. Quadruple ligation of the fistula produced rapid healing of the ulcer. All such specific conditions have been excluded from the subsequent discussion.

In the great majority of cases, there is no one definite pathologic process to which the ulceration can be attributed. Anning in a recent article has emphasized the part played by deep thrombophlebitis in the causation of leg ulcer; and its major importance is tacitly accepted by nearly all writers on the subject. Admittedly most of the patients in the present series have chronic edema of the lower leg and give a history of acute swelling of the leg, whether arising spontaneously or during convalescence from an illness or an injury, which suggests the occurrence of an acute thrombo-

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phlebitis. A considerable number, however, record only a gradual and bilateral swelling of the legs, coming on without obvious precipitating cause. This history was especially common among those who were prisoners of war and had usually been attributed to beriberi. Most workers now agree that it is more likely to have been due to hypoproteinemia. It has often been impossible in careful history taking to make a definite diagnosis of thrombophlebitis; and venographic examination of these patients has on numerous occasions demonstrated a surprisingly normal appearance of the venous circulation.

Characteristically, there is an area of scarring and pigmentation over the lower part of one or both legs; active ulceration may or may not be present; edema is of variable degree, and may be absent; superficial varicose veins may or may not be present. The foot is usually free from ulceration, but fungus infection between the toes is common. The foot may be quite normal in appearance, but is frequently bluish or mottled in color, cold after exposure to room temperature, and with a tendency to sweat excessively. The peripheral pulses are normal unless masked by edema. The cyanosis is increased in the dependent posture, and the color blanches rather readily on elevation, though not so quickly or completely as in recognizable arterial disease. The picture is indeed indistinguishable from that of the characteristic varicose ulcer in the elderly. But these patients are young healthy men, faced with the necessity of earning their living; and the problem of their treatment is an acute and serious one.

This is not a specific condition for which any one cause—not even venous thrombosis—can be invoked. The nutrition of the lower third of the leg and of the scar tissue which has already formed there depends upon a number of separate and only partially related factors. Some of these factors are not amenable to complete correction, while even the completely successful treatment of some of them—the elimination of superficial varices for instance—may not in itself produce healing or guard against recurrence. But if all are resolutely and individually attacked, and even only partially corrected, the over-all balance of nutrition may be so favorably affected as to provide a stable scar which will stand up to sufficient strain to enable the man to earn his living.

FACTORS UNDERLYING CHRONIC ULCERATION

After excluding then such specific recognizable conditions as obliterative arterial disease, chronic osteomyelitis, and the like, what are the factors responsible for the development of ulcers, and for the failure of ulcers, once they have developed, to heal in a reasonable time and thereafter to remain healed?

Venous incompetence. In spite of a tremendous volume of clinical investigation and experimental work, there is still no really clear and undisputed picture of the natural history and evolution of a case of extensive thrombophlebitis, or of the part played by incompetence of the veins in producing ulceration and edema.

Superficial veins.—The skin and subcutaneous tissues of the leg are normally drained of blood chiefly by the veins of the superficial, internal and external saphenous, system. This view has recently been questioned by Cockett and Jones, particularly in relation to the internal malleolar area which is especially prone to ulceration; but it is certainly true for most of the leg. The old name of "varicose ulcer" given to the condition under discussion reflects the view that such ulceration may be due to incompetence of these superficial veins. However, it is now universally accepted that the name varicose ulcer is a bad one and that even severe incompetence of the saphenous system, with obvious back pressure and thrill on coughing, is not by itself sufficient to cause ulceration. The pendulum has overswung from this position, however, and varicose vein operations in cases of chronic leg ulcer have gone somewhat out of fashion. There is indeed fairly wide acceptance of the opinion that operation in these cases, in which thrombosis and obliteration of the deep veins are so often presumed to be present, is dangerous and reprehensible. Numerous tests have been introduced to assess the state of the deep veins and have been reinforced by x-ray examination by various techniques, all with the object of differentiating patients with deep vein ob-

literation and of excluding them from operative treatment of superficial varicose veins. Aird goes so far as to say that either ligation or injection of varicose veins is "forbidden by a history or by physical signs of deep thrombosis whether recent or old." There is ample evidence that a dilated varicose superficial vein, especially in the erect posture, is not carrying any significant volume of blood toward the heart; and its obliteration or ligation will not "throw any undue strain" on the deeper circulation. Collateral channels, probably within the muscle bellies, are so numerous that it is impossible really to cut off the venous return by individual vein ligation; and I have yet to see a case in which superficial varicose vein ligation, properly carried out, has caused an increase in edema or had other ill effect in patients with undoubted deep venous thrombosis. Evidence of deep venous thrombosis may be a contraindication to the sclerosing treatment of varicose veins. It is not a contraindication to their efficient surgical ligation.

The deep veins.—When it became clear that varicosity of the superficial veins was not in itself an explanation of the development of ulceration in the legs, attention was turned to the deep venous circulation. The thesis, first put forward by Homans and developed by Bauer (3, 4), that thrombosis and obliteration of the main deep venous channels of the leg are followed by recanalization with the formation of wide, valveless, incompetent veins, is an attractive one; and it does provide a working hypothesis on which a rational line of treatment may be built up. The evidence for it, however, is roentgenologic rather than anatomic, and it cannot yet be regarded as well proved. It is a factor, however, which should not be ignored in the investigation of these difficult cases.

From experience gained in the treatment of this series of patients I am quite satisfied that venous incompetence per se, whether it be in the superficial or in the deep venous system, is an important mechanical factor—possibly the most important factor—in the maintenance of ulceration, and that it must be corrected and controlled. It should be emphasized again that, contrary to the commonly expressed view, neither obliteration nor incompetence of the deep veins is necessarily a contraindication to the ligation of obviously incompetent superficial veins draining an ulcerated or unstable area. Indeed the effective treatment of the superficial veins alone, even though some deep thrombosis has also occurred, will not infrequently be sufficient to tip the scale in favor of healing. The much more controversial question of deep vein ligation will be discussed later.

Chronic edema. The chronically ulcerated leg is nearly always edematous, especially after standing or exertion. In the early stages the edema is of the pitting variety and varies considerably in extent, subsiding, perhaps completely, after adequate rest in bed. Later a brawny nonpitting induration of the tissues develops which is not materially affected by posture or even by prolonged bed-rest; to it, a variable degree of pitting edema is usually superadded. Just how far this chronic edema is a direct result of deep venous thrombosis or venous incompetence and whether the brawny induration is of a different nature from the pitting edema are questions for argument and for further investigation. But that the edema itself is evil, and a major factor particularly in the recurrence of ulceration, admits of little argument. The treatment and control of edema must play a most important part in the long term management of the ulcerated leg. The specific measures to be taken are discussed later.

Arterial spasm. It must be admitted that the whole subject of arterial spasm is a debatable one. A number of authors have attributed certain of the symptoms of thrombophlebitis, even in its acute phase, to concomitant arterial spasm and have recommended sympathetic blockade or sympathectomy for its relief. The evidence for the occurrence of arterial spasm is indirect, and can rarely be said to be wholly satisfying. Kinmonth has recently laid serious doubt on the validity of the concept of reflex arterial spasm. In most cases of chronic leg ulcer the peripheral pulses are normal; but coldness of the extremity and an unduly rapid blanching on elevation are fairly common findings. There can be no doubt that the venous and arterial circulations in these cases cannot be considered in water-

tight compartments; and particularly in cases with cold extremities, which give a rapid and well marked response in temperature and color to a sympathetic block, the assumption of some degree of arterial spasm is a reasonable one and provides a reasonable basis for a specific line of treatment.

Excessive sweating. This is a feature not uncommonly seen in these chronically ulcerated legs and is worthy of emphasis. It is presumably, like the arterial spasm just discussed, an evidence of sympathetic overactivity. In itself, it may be quite a potent factor in encouraging recurrences, by the resulting maceration of the skin and the facilitation of bacterial infection. I believe that in a number of cases in which improvement has followed sympathetic interruption the benefit is to be ascribed as much to the abolition of sweating as to the more problematic relief of arterial spasm.

Specific bacterial infection. The emphasis laid on the importance of the infecting organisms in the chronic leg ulcer has varied tremendously over the years. With the introduction of almost every new antiseptic or antibiotic, papers have appeared to describe the dramatic effects to be obtained from the use of specific antibacterial treatment. In alternating phases the pendulum has swung away, and the significance of the infecting organisms has been completely discounted. Both views are almost certainly wrong. To rely on any specific antiseptic or local dressing, without correcting the factors of venous stasis and edema, is to invite failure in a large majority of cases. But to pin the faith on occlusive or supporting dressings, or on massage, or on vein ligation, ignoring the nature of the infecting organisms, is at the very least likely to prolong the time necessary to healing. Whatever role the infecting bacteria may play, it has never been suggested that they are beneficial; and it has been my experience that a "combined operation" directed against every possibly responsible factor has far greater chance of success than a regimen which ignores the bacterial flora of the ulcer.

Cleanliness and personal hygiene. This is a matter which should never be overlooked. In a small number of cases it is undoubtedly the absence of personal cleanliness and of ordinary reasonable care of the skin which leads to failure of treatment, in the case of outpatients, or to recurrence after patients have left the hospital. A large proportion of these patients suffer from fungus infections of the feet and toes. These, if not properly cared for, lead to weeping eczema of the feet, chronic fissure, macerated skin, and secondary edema, which may play an important role in encouraging recurrence. I have one patient, a mental defective, who has been repeatedly healed of his ulceration with the edema well controlled and yet is constantly in and out of the hospital on account of recurrent skin infections arising from this cause.

General health. Attention to the general health, correction of anemia or undernutrition, is a part of the treatment of leg ulcer. It is in only a small proportion of patients that it plays a major role; but anemia, malnutrition, and subclinical vitamin deficiencies should be carefully looked for in patients who should respond to thorough treatment yet fail to do so. Numerous workers have established the importance of this factor in the case of tropical ulcer, and there is no reason to doubt that it may play a similar part in the condition now under discussion.

Psychologic factors. This aspect of the ulcer problem is involved and largely unexplored but requires consideration on a number of different scores. These patients are often "difficult" patients. I believe that the psychologic difficulties are mostly secondary rather than primary, results rather than causes; but they introduce important problems nevertheless, and call for much patience and tact. Prolonged pain and inconvenience, the slavery of daily dressings, a hopeless attitude on the part of previous medical attendants, the mess and the smell, all tend to make the patient introspective, to make him an authority on his own treatment, unwilling to accept new regimens, and reluctant to persevere with a course of treatment which is not dramatically successful. A certain number, as many as 3 in the series here considered, have become wed to their ulcers, have learned to live with them without great inconvenience, and have no real desire to be healed. A careful consideration of the psychologic make-up of the patient and

his attitudes may be of great assistance, not in deciding on a line of treatment, but in gaining his co-operation. Replacing the air of hopelessness by one of guarded confidence may play a decisive part in the cure; and the superficial type of psychotherapy required for this purpose should be neither scorned nor evaded by the surgeon who undertakes to treat these patients. More difficult is the question of self-induced lesions, artefacts, and deliberate malingering. Exaggeration of symptoms and disabilities by work-shy patients in my experience is not common, but it is by no means unknown; and the surgeon should be on the lookout for it. Deliberate induction of an ulcer by friction or other means is rare but must also be borne in mind.

Economic and environmental conditions. These too must come within the purview of the surgeon treating these lesions. In a certain number of cases, recurrent ulceration will occur after every line of treatment has been thoroughly pursued and the patient comes to be regarded as incurable. Few of these incurables are really so if their living and working conditions can be satisfactorily adjusted. The aim of treatment should of course be to restore the patient to his normal working and earning capacity. Where this proves impossible, a change of occupation to something sedentary, perhaps involving some definite course of training at a rehabilitation center, may temper the wind to the shorn lamb. If it appears that a complete reorganization of the patient's life is to be necessary, the position should be put to him without undue delay, before he is too old or too discouraged to take the necessary action.

ROUTINE OF INVESTIGATION AND TREATMENT

Patients with chronic leg ulcer present a varying clinical picture and show a varying response to treatment. Some will respond rapidly to simple and uncomplicated treatment; even patients who have a long history of breakdown and recurrence may prove amenable to conservative nonoperative measures; and it is quite unnecessary to subject every patient to the exhaustive series of investigations which may ultimately prove necessary in the complicated intractable case. It is our policy in this department to proceed a step at a time. An occasional patient may thereby suffer several admissions to hospital and some delay in final healing; but many others will be saved unnecessary and sometimes rather unpleasant investigations, and the number of ulcers healed in a given year will be increased rather than diminished by making haste slowly. The history and the first full and careful clinical examination should suffice in nearly all cases to determine the immediate line of treatment—the necessity of admission to hospital, of rest in bed, and of the operative treatment of varicose veins. Further than this it is unnecessary to go.

History. There is little that requires special emphasis here. If the history is routinely and conscientiously taken, few relevant facts are likely to be missed. The onset, of course, is important; the occurrence of precipitating injury, the time relationship of ulceration and edema, the history of previous operations—notably varicose vein ligations and skin grafting operations—and the exact nature of their postoperative course, are all points which may be helpful in making a prognosis and deciding upon treatment. A history of clinically diagnosable thrombophlebitis, for example following pneumonia or dysentery, should be sought for. Such cases usually have a worse prognosis and call for more intensive treatment than those in which thrombosis has been a secondary occurrence after injury or ulceration. The exact nature of all treatment which the patient has received should be very carefully scrutinized. Causes of failure in the omission of small but important details may be unearthed. One should not be discouraged from using a particular line of treatment, for instance occlusive elastoplast bandaging, just because the patient says it has been tried before and failed.

Physical examination. A cursory examination of the legs of the patient is never justified, and the trouble of establishing for oneself a definite routine of examination, or even a formal schedule of points to be noticed will be amply repaid.

The general physical examination of the patient requires no special notice here but must not be neglected. Special attention should be paid to the cardiovascular system,

the signs of anemia, and evidence of malnutrition, past or present. A Wassermann or Kahn reaction should never be omitted, though no case of syphilis was seen in the 120 patients studied here.

The actual examination of the legs must be carried out with the patient stripped from the waist down, and in the erect and the recumbent posture. To attempt to assess treatment requirements from a hasty examination of the one affected leg with the trouser leg pulled up above the knee is to invite mistakes which may cost the patient much time and trouble. This thorough examination, which actually takes only a few minutes once the routine is established, must be done at the first interview and not merely when treatment has failed or when the patient has returned with a recurrence.

The ulcer itself is often the least important feature of the examination. It should, however, be carefully described, and preferably drawn to size, on the case record. Regional glands should be palpated, and the possibility of malignant change in a chronic ulcer should always be borne in mind.

Apart from the ulcer, the points to which specific attention should be paid lie chiefly in the feet rather than in the legs. They are: color, and its response to elevation and dependency; the peripheral pulses, with their response to exercise; skin temperature: a marked difference between the two feet, or a sudden fall in the temperature gradient at about ankle level; (It should be noted that the presence of an acutely inflamed ulcer may well raise the temperature of a foot by several degrees.) edema, its extent and nature; (If necessary, a patient's statement as to the degree of swelling should be checked by re-examination at the end of a day of normal activity.) the presence of dilated or varicose veins, whether directly related to the ulcer or not; the position of the scars of previous operations.

If these various points are specifically noted and recorded at the first examination, it is rare that anything further is required to allow the first stages of the plan of treatment to be formulated. It is in the case which has recurred after adequate primary treatment and in spite of the conscientious observance of the safeguards against recurrence that the more special investigations referred to now may be required.

Venography. A large literature has grown up around this subject, which will not be discussed in detail in this paper. The great variety of techniques which have been described is an indication of the difficulties of the subject, and most roentgenologists will agree that the interpretation of films is fraught with pitfalls. Dow's valuable paper, in particular, emphasizes the uncertainties of this method of investigation (9).

Most writers on the subject of venography have been chiefly interested in its use in demonstrating either the patency or the competency of the main deep venous trunks. It is in this respect that the main difficulties of interpretation arise. It is my opinion, after an experience of 85 venograms carried out by a variety of techniques—chiefly that of Dow and the retrograde technique of Lockhart-Mummery and Smitham—that the greatest caution must be used in drawing conclusions from the roentgenograms, particularly when the main venous trunks—the popliteal and superficial femoral veins—fail to fill or are incompletely visualized. I do not believe that with any technique, however carefully carried out, the absence of filling of deep venous trunks can be taken to infer with any certainty that they are either thrombosed or obliterated, while Dow has conclusively demonstrated the fallacies of the retrograde injection method. Positive findings, on the other hand, may yield most valuable and helpful information. A good venogram will accurately localize the site of an incompetent perforating or communicating vein, or may demonstrate an unsuspected dilated external saphenous vein. Dow in a later paper (10), has convincingly shown the value of roentgenography in elucidating the causes of recurrence of varicose veins after operative treatment. Well made venograms in this type of case may give most useful information in the planning of further surgical treatment. Dilatation and tortuosity of the main popliteal venous trunk may also be demonstrated; and this information may be a deciding factor when the (rarely indicated) operation of popliteal vein ligation is being con-

sidered. Venography is a rather uncomfortable investigation for the patient. In 4 of my cases it was followed by an extensive and painful superficial thrombophlebitis. This in no case did any harm, but it introduces an uncertain, and perhaps uncontrollable, factor into an already difficult problem. I therefore use it only when it seems likely to yield positive information of the kind noted, never merely to demonstrate the patency of the deep venous channels which can be more accurately assessed by purely clinical methods.

Venous pressure measurement. Direct measurement of the venous pressure in the foot was suggested by de Takats as early as 1929, and has been used recently by a number of American workers investigating the ulcer problem. Walker has shown the significance of a comparison of the levels at rest and during exercise and recommends the test especially for cases in which popliteal vein ligation is being considered. Theoretically, and if the hypothesis of recanalization and incompetence of deep veins is accepted, this should be a most useful and objective test; but after some initial enthusiasm I have given it up except in a few very special cases. The technique is by no means so simple as might be expected; the readings are subject to a very large experimental error; an incision in the foot is nearly always necessary, and these feet are not lightly to be incised unless information of a really practical nature is to be gleaned from the procedure. Unless a ligation of deep veins is contemplated the test does not yield results commensurate with its risks and discomforts; and even in these cases I now rarely use this investigation.

Skin temperature measurements. It must be emphasized that in any case in which simple estimation of skin temperature with the back of the hand reveals suggestive departure from the normal, the patient must be re-examined after the feet and legs have been exposed to room temperature (preferably under 22 degrees centigrade) for at least 40 minutes. Without this precaution such measurements lack all validity and may seriously mislead. The effect of an acute ulcer in raising the temperature of its surroundings has already been noted. I use the Cambridge six-lead instrument; and measure first the comparative temperatures of the two limbs at corresponding levels, and then the gradient from groin to toes. The response of the temperature of the toes to an intravenous injection of priscol may sometimes indicate a worthwhile line of treatment.

Sympathetic block. Most patients showing significant skin temperature changes are further tested for their response to a paravertebral novocain block of the second and third lumbar sympathetic ganglia on the appropriate side. The thermocouple is used to measure and record the nature of the response; but as with the temperature measurements themselves, a change that cannot be unmistakably recognized with the eye and the fingers is unlikely to prove a safe guide to treatment. A *rapid* rise in skin temperature of the order of from 5 to 7 degrees centigrade, accompanied by a change in color from blue to pink does give some reasonable ground for expecting that sympathectomy may effect some worthwhile improvement.

Arteriography. This investigation is only rarely indicated in this group of patients. Its use in this series has been confined to those cases in which the clinical findings suggest the presence of organic arterial narrowing, where it serves to confirm the diagnosis, and so to remove the patient from the category now under consideration.

TREATMENT

The treatment of these patients may conveniently be divided into three phases: the healing of the ulcer, the prevention of recurrent ulceration, and, all too frequently, the treatment of recurrences which occur despite the measures taken to prevent them. It is to the patient's advantage that the three phases be kept fairly separate in the surgeon's mind, and that treatment should proceed a step at a time. Only a small proportion of patients need the detailed investigation and treatment called for by the most difficult cases.

Healing of the ulcer. It is common knowledge that nearly all these ulcers will heal on a simple regimen of rest in bed and local dressings. The process, however, is time-consuming and the resulting scar, often thin and unstable.

Opinion has, therefore, hardened against this method of treatment, and widespread reliance has been placed on methods which keep the patient on his feet, or even about his daily work. First popularized in Great Britain by Dickson Wright, the "closed" elastoplast technique has now been used in many thousands of cases and has saved an incalculable number of man-hours and hospital beds and a vast amount of cottonwool and lint. In the classic varicose ulcer of the general outpatients department, I yield to none in my respect for this method of treatment. However, I have been unable to reproduce in these ex-service patients the results obtained by closed and ambulant techniques. Severe elastoplast reactions have been common: a widespread contact dermatitis which does not, in spite of the statement of many enthusiasts to the contrary, improve spontaneously if treatment is persisted in; the rapid, almost mathematical, diminution in size of the ulcer has not occurred; and many ulcers have recurred while the patient was still wearing the elastoplast.

The alternative then is bed-rest; and I have been reluctantly driven to accept this as the best, and in the long run the most economical, method of treating these patients. The enthusiast for elastoplast treatment will no doubt continue to use it; but I would urge that unless response is rapid it is wrong policy to persist in it. This applies especially to the patient with pitting edema. Bed rest is the treatment for this condition, and its efficacy is greatly enhanced by raising the foot of the bed on 8 inch blocks to lend the aid of gravity in the dissipation of the edema.

Bisgaard introduced the use of massage into the treatment of these chronic ulcers. It is in my opinion the most valuable single adjunct to bed-rest in the acceleration of healing, and, more important, in the production of a stable scar. I do not use it as a routine measure but introduce it early into the treatment of every case which is not responding rapidly to simple rest and elevation. The treatment consists in the daily use of extensive massage, applied to the whole lower limb, commencing proximally and culminating in heavy localized massage of the water-logged tissues immediately round and beneath the ulcer. The sine qua non of its success is an enthusiastic and conscientious physiotherapist, who will follow the quite strenuous technique originally set out by Bisgaard. At the end of each treatment session—the massage is administered twice daily in severe cases—a local dressing with a neutral cream is applied. The British Pharmacopoeia preparation ung. alcohol lanae, with about 10 per cent of added water to reduce "stickiness" has proved very satisfactory for this purpose. This application is varied by the addition of antibiotics if the bacteria present in the ulcer call for specific therapy. A very firm and strong elastic bandage is then applied from toes to tibial tubercle. Treatment is continued daily, not only until the ulcer is healed but until the scar itself is able to withstand the not inconsiderable trauma of the local massage without blistering or breaking down.

The number of local applications which have been recommended for the treatment of ulcers is legion. Contrarily, opinion has often hardened into a skepticism that the nature of the local application is immaterial. This view has of course gained strength from the fact of the rapid modification of the ulcer flora which often occurs under simple elastoplast treatment. While maintaining in general this healthy skepticism, I do feel that local medicaments have their place, notably in the treatment of Pseudomonos pyocyanea and Bacillus proteus infections and in cases in which gram-positive cocci fail to disappear under simple dressings. It is my practice to have a full bacteriologic examination made on all ulcers which do not show satisfactory evidence of rapid healing after the usual contributory factors have all been corrected—edema controlled and varicose veins ligated. The infecting organisms are identified, and their sensitivity to the four usual antibiotics and also to aerosporin (polymyxin) is estimated. Local applications of streptomycin or chloramphenicol are occasionally of use in clearing up a chronic infection. In the pyocyaneus infections I have found the use of aerosporin ointment extremely efficacious, in refreshing contrast to most other available means of attacking this persistent and resistant invader, and in numerous cases a sluggish and unresponsive ulcer has commenced to heal when this organism has been

banished. In this connection, I have found specific treatment a valuable adjunct to the Bisgaard regimen, the neutral ointment being replaced by one containing aerosporin or other appropriate antibiotic. Numerous authors have described the good results obtained by various antiseptics and antibiotics, the latest report being that of Shaw and Troensegaard-Hansen on the use of chloramphenicol in propylene glycol. The error to be avoided is that of relying on a specific medication, and neglecting the many and varied factors which play so much more important a part in preventing healing. Organisms may be banished from an ulcer with comparative ease; they will return or be replaced by others unless these underlying factors are corrected.

Prevention of relapses. In the majority of cases the simple measures described will effect healing in at most a few weeks, and patients should be spared unnecessary examination and treatment at this stage. In the prevention of recurrences, the one factor of vital importance is undoubtedly the provision of adequate support to prevent the redevelopment of edema and venous stasis. For this purpose elastic stockings are essential; and if properly prescribed, faithfully worn, and adequately maintained, they provide an effective safeguard against relapse. Failure to attend to detail, however, either in prescription, use, or maintenance, leads to inefficacy and brings the use of elastic hose into unwarranted disrepute. One sees so many examples of patients fitted with unsuitable types of stocking, and of patients inadequately instructed in their use, that it seems worth while to set down in some detail the practical points in the use of elastic hose which have been impressed upon us by our experience here.

It is an absolute essential that the measurements for stockings be taken only after all edema has been dispelled; this means, at the very least and in the mildest case, after the patient has had 24 hours in bed with the foot of the bed raised on blocks. Casual measurements of up patients in the outpatient department or in the doctor's surgery can only lead to ill fitting stockings and to poor results. Manufacturers supply forms for the recording of measurements, and their instructions should be closely observed. Above-knee and thigh-length stockings are, in the patients now under discussion, practically never called for. They are useless without suspenders and suspender belts, which few male patients will wear; and by creasing they may form constriction bands which do more harm than good. The stocking should come up to, but no higher than, the tibial tuberosity and should require no "turn-down" to allow of full knee flexion. At the other extremity, it is most important that the stocking reaches right to the base of the toes. Manufacturers' forms seem to take no cognizance of the varying length of the human foot, and it is most important to record the length from heel to end of stocking so that allowance can be made for this factor. A stocking too short in the foot allows of swelling at the base of the toes which causes discomfort and leads patients to discard their stockings as ineffective.

The most effective stocking in my experience is the light drab, one-way stretch material, with open heel. These are easy to put on, durable, and do not easily ruck or crease. Patients with severe pitting edema or with ulcers below the malleoli require a closed heel. Even then the seams may irritate the tender scar tissue in this position; patients should be advised to wear the stocking inside out to avoid this. In a few patients this quality of stocking seems to irritate the skin or to cause undue sweating. A lighter stocking, usually of the two-way stretch type may then be prescribed, or, in extreme cases an elastic net, which, while less strong and effective, may be tolerated when anything else precipitates dermatitis. Small ulcers and small patches of eczema may be dressed under elastic stockings, but if extensive dressings are necessary it is more convenient and effective to replace stockings by strong elastic bandages of the type used during the Bisgaard treatment.

It is essential of course that patients wear the stockings *always*, putting them on before rising in the mornings and removing them only on retiring at night. Duplicates should always be provided to allow of washing as required, and patients must be warned to apply for replacements before the stockings become overstretched. It is an important point that re-

newals should likewise be made in duplicate; otherwise the patient will find that his new stocking is too tight after he has been wearing an old duplicate.

The presence of varicose veins is noted at the time of the original examination. Their treatment is rarely necessary to secure healing of the ulcer but should always be carried out as soon as the ulcer is healed and before the patient is discharged from hospital. I am sure that the treatment of such varicose veins, as already discussed and largely independent of the state of the deep venous circulation, is an essential part of the primary management of these cases and should not be deferred until recurrence of the ulcer forces its necessity upon the surgeon.

The treatment of relapses. Finally, there is the problem of the patient whose ulcers recur after successful healing and in spite of apparently adequate precautions against recurrence, such as the surgical cure of varicose veins and the fitting of elastic stockings. These patients are investigated fully by all the ancillary methods discussed in the second section of this paper, and a resolute attempt is made to pinpoint the factor responsible for recurrence. The factors which may be brought to light in such "doubly recurrent" cases, and whose correction may still lead to ultimate cure are:

1. Varicosity, dilatation, and incompetence of the external saphenous vein, which have not been recognized at the initial examination. I have found venography of special value here; in fat legs, particularly, a dilated external saphenous vein may easily escape attention. A carefully made venogram will nearly always demonstrate its presence, and I have notes of several cases in which its treatment by ligation and retrograde injection has led to healing of a recurrent ulcer.

2. Recurrent varicose veins. However carefully and thoroughly a varicose vein operation may be done, occasional patients will show recurrence due to progressive incompetence of communicating veins. Even commoner is the recurrence which is really due to an inadequate primary operation. Dow (10) in a recent paper has well outlined the different types of recurrence which occur. Venography is again of considerable assistance in accurate diagnosis. One should never be ashamed to admit that a varicose vein operation may need doing again, nor hesitate to advise operative treatment on the grounds that it had previously failed.

3. Deep vein incompetence. Considerable enthusiasm developed a year or two ago for the operation of deep vein ligation in cases of recurrent ulcer in the postphlebitic leg. The earlier reports do not appear to have been followed by the corroborative after studies which might have been expected if the successes of the operation were as real as was at first apparent. I have adopted an attitude of the greatest caution in regard to this operation; but I do feel that there are occasional cases in which it may prove of value, at least for a period of some years. Its limitations must, however, be clearly recognized, and the indications strictly defined. The "bursting leg" syndrome has not in my experience been as common as the earlier papers suggested; but it is in this type of case, provided corroboratory evidence of deep venous incompetence can be secured, that the operation seems to give its most favorable results. It should certainly not be performed for chronic edema alone as edema may be increased rather than diminished after it. I have come to require the fulfillment of four criteria before accepting a patient for ligation of the popliteal vein; namely, (a) chronic or recurring ulceration not responding to other less radical treatment including the obliteration of all superficial varicose veins; (b) severe and crippling pain, especially if it is of the "bursting" type; (c) absence of severe edema; (d) positive venographic evidence of dilatation and irregularity of outline of the popliteal vein. Adhering strictly to these requirements, I have only had occasion to tie the popliteal vein in 9 of the 120 patients discussed in this paper. My results have been very similar to those described by Moore; and my present opinion, like his, is that if patients are very carefully selected according to strictly defined indications the operation is a valuable one and will secure healing in a number of cases after all other methods have failed.

4. Sympathetic overactivity. Sympathectomy has been advocated on numerous occasions for recurrent ulceration, and most surgeons can point to some successes, at least in

the early postoperative period. Haxton, using the "chemical" method of sympathetic interruption, reported some very favorable results. It appears to be a common experience that a longer follow-up tempers the enthusiasm for this mode of treatment. I believe, however, that even temporary relief, if it is measured in years and not merely in months, is not to be lightly disregarded. I do the operation (high lumbar sympathectomy) in doubly recurrent cases when the foot is blue and cold, the peripheral pulses poor, sweating excessive, and when a novocain sympathetic block produces a *rapid* and marked rise in skin temperature and change in color.

5. Skin grafting. Once all the other unfavorable factors have been corrected, recurrence may still take place owing to the thin, vulnerable nature of the scar over the tibia. Full thickness skin replacement in these cases may give most satisfactory results: but if the vascular status of the leg is unsatisfactory, its success is likely to be only temporary. A number of patients in this series had had one or more skin grafting operations of various types. In almost all of them new ulceration had occurred, usually at one corner of the graft.

6. Change of occupation. In a few cases ulceration recurs after every possible precaution has been taken and after every diagnosable abnormality and predisposing factor have been dealt with. The provision of a sedentary occupation, even though it involves special training and a complete reorganization of the patient's life, must then be seriously considered. In 2 patients in this series such a procedure has led to a sudden cessation of ulceration and pain and a tremendous improvement in the patient's economic and financial position. In 3 more, I am sure the same result would follow if only the patients could be brought to take this radical step. Mere light work is not enough; the job must be one in which the man is really sedentary, and preferably one in which he can keep the leg elevated while he is working.

SUMMARY AND CONCLUSIONS

The incidence of chronic and recurrent so called varicose ulceration of the legs is especially high in young ex-servicemen of the age group 30 to 45 years and presents a problem of great economic and social importance.

Neither the term varicose nor the newer fashioned one, postphlebitic, fully expresses the etiology of this recurring ulceration. It is believed that the adequate nutrition of the lower leg depends upon a number of different factors, some of which have been by no means fully evaluated. While it may be impossible fully to correct the abnormalities resulting from deep venous thrombosis and its sequelae, it is often possible, by paying attention to detail, so to improve the over-all condition of the leg that the balance is tipped in favor of healing. Exclusive attention to only one factor, even though it be the overbearingly important one of venous incompetence, may of itself fail to produce this happy result.

An appeal is made for a more eclectic and more carefully planned attack in the treatment of these cases; and the opinion is expressed that there are few if any who cannot be restored to efficient wage-earning capacity.

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OCCULT CARCINOMA OF THE BREAST

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THE presence of enlarged axillary lymph nodes with no other evidence of disease brings up a very interesting problem of diagnosis and treatment. It is obvious that the primary problem is diagnostic, and the solution will undoubtedly involve removal of tissue for microscopic examination in many instances. There are numerous abnormalities which are manifested by enlargement of lymph nodes. The selective enlargement of the axillary nodes or, even more specifically, the enlargement of one set of axillary nodes reduces the possibilities considerably. It is the metastatic neoplasms, specifically, adenocarcinoma primary in the breast, with which this paper is concerned.

For the purposes of our study, "occult carcinoma of the breast" implies histologically proved carcinoma of the breast with axillary nodal involvement in a patient who has manifested no signs or symptoms of any abnormality of the breast. For new information on this subject, we studied the clinical and pathologic material from such cases observed at the Mayo Clinic from 1907 through 1950. An effort was also made to compare such data with those obtained from a study of carcinoma of the breast in general.

BACKGROUND DATA

The spread of cancer of the breast to distant sites without clinically evident disease of the breast has been recognized for many years, but only recently has there been a renewed interest in the problem.

As early as 1907 Halsted wrote: "I have twice seen extensive carcinomatous involvement of the axilla due to mammary cancer which, later, in neither instance became demonstrable for a considerable period after the axillary glands had attained conspicuous dimension. In each case the 'axillary tumors' had been removed, in one of them a year before and in the other perhaps 2 years prior to my first examination, which though made in the most careful manner, failed to find the slightest evidence of cancer of either breast. In the course of a few months thereafter, the mammary disease manifested itself in both patients." Halsted also described a third patient operated upon for enlarged axillary nodes who returned 2½ years later because of recurrence in the axilla. Only at this time was an "indefinite" lesion found in the breast.

Cameron said that the small size of the primary growth is by no means an indication of its recent origin, and he concluded from experience that some mammary cancers metastasize before they become clinically evident. He remarked that obviously slow-growing tumors might not metastasize for long periods of time. He reported 3 cases of enlarged axillary glands which were removed months before the appearance of a primary tumor of the breast was noted.

Several other similar case reports are those of Primrose, Cheatle, Cheatle and Cutler, Shore, Willis, Cogswell, and Klopp.

Shore reported an interesting case in which the tumor had undergone gelatinous degeneration with areas of calcification in the tumor tissue. He expressed the belief that this was evidence that the growth had been present for a long time even though there was no clinical evidence of a growth in the breast.

In the recent literature, Jackson has been credited with initiating renewed interest in this problem in his report of 3 personal cases. In 1951, Weinberger and Stetton reported a series of 5 such cases.

As early as 1909, Cameron had recommended the removal of the breast when operating for a malignant axillary node even though no tumor

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in the breast could be detected. Jackson reaffirmed this belief, but cautioned one to evaluate the patient well before mastectomy to rule out other possible primary sources, since it is not uncommon for primary tumors of other organs to metastasize to the axillary nodes while such tumors are still not clinically evident.

Fitts and Horn recently cited 15 cases in which the breast was removed without palpable evidence of a tumor. The initial signs were as follows: enlarged axillary nodes, 4 cases; discharge from the nipple, 4 cases; dermatitis of the nipple, 4 cases; edema of the skin, 1 case; retraction of the skin, 1 case; and distant metastasis (orbit and abdominal viscera), 2 cases. In each and every one of these cases a primary tumor was subsequently found in the breast. Other instances of visceral and skeletal metastasis from primary tumors of the breast without demonstrable clinical evidence of a tumor in the breast have been reported by Horwitz, Johnson, Ginsburg, Neal and Robnett, and Willis.

This entity is undoubtedly not as rare as reports in the literature would indicate. Many physicians perhaps have seen or had contact with similar cases, and for this reason the problem is recognized as being of general interest.

MATERIAL AND METHOD

The clinical, operative, and pathologic records of 5,451 cases of mammary cancer were reviewed. These consisted of operative cases of histologically proved carcinoma of the breast in which there was axillary nodal involvement. From this group, those cases which fulfilled the aforementioned criteria for the diagnosis of occult carcinoma of the breast were selected.

Data on age, sex, race, past history, familial incidence of cancer, associated illness, and symptoms related to the breast and axilla were recorded. Also, data on the duration, size, location, consistency of the axillary lesions, and the results of a very careful review of information pertinent to examination of the breast made by at least three separate examiners were tabulated. In addition, details of the early and late postoperative course and the results of long term follow-up studies were recorded for comparison.

The tissues removed at operation, which were preserved in 10 per cent formalin and were fortunately all available, were examined grossly. The size, location, consistency, and gross appearance of the primary lesion of the breast were noted as were the similar characteristics of the axillary nodes. Blocks of tissue were removed from the primary lesion and other representative parts of the breast, and also from several axillary nodes. Sections prepared from these blocks and stained with hematoxylin and eosin were studied with any original slides made at the time of operation.

Of the 5,451 cases in which there was proved carcinoma of the breast with axillary nodal metastasis, 27 fulfilled the criteria necessary for the diagnosis of occult carcinoma of the breast. Of this group, 2 were subsequently excluded because the specimen that contained the primary lesion of the breast was not available. Data were, accordingly, based on the remaining 25 cases.

FINDINGS

The incidence of occult carcinoma of the breast in this large series was slightly less than 0.5 per cent. Since involvement of the axillary nodes is encountered in about 66 per cent of all cases of mammary carcinoma at the Mayo Clinic, it is evident that approximately 0.3 per cent of all patients with carcinoma of the breast have the occult form of the disease.

Age and sex. The youngest of the 25 patients was 30 years of age and the oldest was 69. The mean age was 49.9 years. Twenty-four of the patients were women. The 1 man in the group was 42 years of age.

Symptoms. There were no symptoms referable to disease of the breast in 24 of the 25 cases. One patient had slight watery discharge from the nipple for 2 years prior to radical mastectomy. Twenty-two patients presented the specific complaint of a mass in the axilla. Two of the 25 patients were seen either for routine examination or for some unrelated condition and were discovered to have enlarged axillary nodes at the time of examination. The axillary enlargements had been noted for less than 6 months by 22 of the 25 patients, while the remaining 3 had noted enlarged nodes for more than 2 years.

Physical findings. In accordance with the criteria for the selection of these cases, in no instance was there a palpable mass in either breast, nor were there any overlying abnormalities of the skin or evident disease of the nipple. The enlarged axillary nodes present in all cases varied in size from small discrete nodules to large matted masses with fixation to the skin of the axilla.

In 10 cases there had been a previous biopsy of the enlarged axillary nodes elsewhere. One patient had undergone surgical removal of a single axillary node 2 years previously and again 1 year prior to her having been seen here. There was recurrence of the tumor on each occasion.

In each of the 10 aforementioned cases, a slide or tissue was available for study before radical mastectomy was carried out, and a diagnosis of adenocarcinoma, metastatic to the axillary nodes, was established.

There were no other enlarged nodes and no other important physical findings related to this problem.

Treatment. Several different surgeons were responsible for the care of these patients. Twelve patients had biopsy of the axillary nodes at this clinic, followed by radical mastectomy. Ten patients had a biopsy of the axillary nodes elsewhere; microscopic confirmation of the diagnosis at this clinic was followed by radical mastectomy. Two patients had a "primary" radical mastectomy without previous biopsy of the axillary nodes, and 1 had a semiradical mastectomy without previous biopsy of the axillary nodes.

In 1 of these cases, a diagnosis of adenocarcinoma metastatic to an axillary node was made from a biopsy specimen taken elsewhere, and the patient underwent laparotomy because of an abdominal mass. This was proved to be an enlarged right lobe of the liver, and the patient subsequently underwent radical mastectomy with demonstration of the primary lesion in the breast.

Postoperative course and follow-up. The postoperative course in all 25 cases was essentially uneventful. All but 1 patient received routine postoperative roentgen therapy. Follow-up data on the subsequent course were available in most instances through records of subsequent visits or letters to the patient or relatives.

Eighteen patients were treated 5 or more years prior to this study. Nine of these 18 patients survived 5 or more years after radical mastectomy and roentgen therapy. Of these 9, only 1 subsequently died of metastatic carcinoma, and this death occurred 10 years and 3 months after treatment. The remaining 8 were either alive at last report or dead of some other cause. Twelve patients were treated 10 or more years prior to this study, and 6 have survived 10 or more years.

Nine of the 25 patients in this study are dead as a result of their carcinoma. One patient died of pulmonary embolism 3 months postoperatively, and 1 died of congestive heart failure 25 years after operation. One patient died 17 years after operation, from causes unknown.

Six patients of the entire group have survived 10 years or more and 4 patients have survived 15 years or more without evident recurrence of the carcinoma. The longest survival with recurrence is 10 years and 3 months, and the shortest survival with recurrence is 10 months.

Pathologic findings. Gross features.—Owing to the small size of the primary lesion in the breast and to the poor state of preservation of some specimens, the gross characteristics were not always recognizable. Of the original 27 surgical specimens available for examination, no gross tumor could be seen in 7. A review of the pathologic reports revealed that in 3 of these 7 cases there was no gross evidence of tumor in the fresh specimen, the diagnosis having been made microscopically and the slides having been preserved. Multiple blocks were cut from the remaining 4 specimens. In 2 of these 4 cases microscopic evidence of tumor was found in the breast tissue, and in the other 2 cases no evidence of a primary lesion could be detected, presumably for reasons mentioned in the first sentence of this paragraph. Since microscopic slides could not be located in these 2 cases, they were excluded from this study.

Twenty specimens, then, were suitable for gross study of the primary lesion and of the nodes.

It was not always possible to determine the location of the primary lesion. Two of the lesions were only a short distance beneath the nipple and the remainder were deep in the breast tissue. The location of the lesion could be definitely ascertained in 12 specimens. In 7 of these, the growth was located deep in the midportion of the breast. In 5 it was situated deep in the upper and outer quadrant of the breast. In 1 specimen the lesion was found at the very edge of breast tissue in close proximity to the involved chain of nodes leading into the axilla.

The size of the lesions in the breast varied from "no gross tumor visible" to masses measuring up to 2 centimeters in diameter. In 20 instances the lesion was less than 1 centimeter in diameter and in 14 it measured 5 millimeters or less. Five tumors were more than 1 centimeter in diameter but less than 2 centimeters. In 2 instances, 2 gross nodules, measuring 5 millimeters and 2 millimeters, and 4 millimeters and 2 millimeters, respectively, were in close proximity. Three tumors were of microscopic size.

The gross examination revealed a definite, firm, grayish-white nodule in only 8 cases. In 3 there was present a slight diffuse firmness as compared to the consistency of the surrounding breast tissue. In the remaining cases there was no definite gross evidence of tumor. In 7 cases there was diffuse or localized thickening of the breast tissue characteristic of fibrous mastitis. This will be described further under microscopic findings.

The axillary nodes were, of necessity, grossly involved, although as mentioned previously, 10 patients had been operated upon elsewhere with removal of one or more of these secondary deposits.

Microscopic characteristics.—The distribution of the cases according to grade (Broders) of lesion was: no cases in grade 1; 2 cases (8 per cent) in grade 2; 8 cases (32 per cent) in grade 3; and 15 cases (60 per cent) in grade 4. It will be noted that 92 per cent of the cases were in grades 3 and 4.

Histologically, the great majority of lesions (75 per cent) were of the comedocarcinoma and medullary adenocarcinoma types. There were 11 cases of comedocarcinoma; 7 of medullary adenocarcinoma; 3 of scirrhous adenocarcinoma; 1 of alveolar carcinoma with areas of comedocarcinoma; 1 of mucous adenocarcinoma; 1 of carcinoma simplex; and 1 of adenocarcinoma, papillary type. The types mentioned are not necessarily pure types but the predominant feature was used to classify these lesions.

Infiltration of lymphocytes about the periphery of the lesion was noted in 7 cases, and this was especially marked in 3. The lesions in which this phenomenon occurred were of the comedocarcinoma and medullary adenocarcinoma types.

Among the associated pathologic conditions, fibrous mastitis was present in 7 cases, sclerosing adenosis in 2 cases, Schimmelbusch's hyperplasia in 3 cases, intracanalicular fibroadenoma in 2 cases, benign papillomas in 1 case, and grade 1 papillary adenocarcinoma in 1 case.

One breast was found to contain a benign papilloma, a grade 1 papillary adenocarcinoma, and a grade 3 comedocarcinoma with marked lymphocytic infiltration. Several other breasts exhibited more than 1 associated benign lesion.

In 1 lesion there was microscopic evidence of calcification associated with grade 3 comedocarcinoma.

COMMENT

The mean age of 49.9 years for the patients in our series corresponds closely to the mean of 51.2 years reported by Harrington (11) and 53.7 years reported by Hawkins in over-all series of carcinoma of the breast.

It is interesting to note that there was 1 man in this group. We were unable to find the report of a single case of this type in the literature. Approximately 1 per cent of all cancers of the breast occur in the male, according to Horsley, Schmid, Williams, and Harrington (10). It would seem reasonable to assume that carcinoma of the breast would be discovered more easily in the male than in the female, thereby reducing the possibility that carcinoma of the breast would be occult in the male.

The incidence of occult carcinoma of the breast as defined in this study has not been

stated in the literature. Undoubtedly this type of lesion is quite rare, as our own data indicate. It remains of interest, however, because it presents a challenge to correct diagnosis and therapy.

Apparent primary enlargement of the axillary lymph nodes is due to a number of causes, but metastatic carcinoma is the most frequent single cause according to Joss. He studied 84 cases of apparent enlargement of the axillary nodes and found the following distribution: small cell lymphosarcoma 6 cases, reticulum cell lymphosarcoma 5, Hodgkin's disease 10, giant lymph-follicle hyperplasia 3, tuberculosis 16, metastatic malignancy 18, melanoepithelioma 5, axillary breast tissue 1, neurofibroma 1, and inflammatory condition 9, and normal condition 10. The 18 cases of metastatic cancer included 13 females and 5 males. No apparent primary lesion was discovered on clinical investigation by at least three examiners.

The location of the primary malignant lesion was discovered by Joss in 4 females: 3 had a primary lesion in accessory axillary breast tissue while the other had a small primary lesion of the breast as disclosed on pathologic examination of the removed breast. Nine patients had neoplasms of grade 4 malignancy, type and source undetermined. Seven of these 9 patients died within a year, and 2 were alive after 6 months but there was no further follow-up. The cause of death was not known in these 9 cases. Of the 5 male patients, 1 was later found to have a primary squamous cell carcinoma of the hand, and the remaining 4 were considered to have neoplasms of grade 4 malignancy, type and source undetermined.

Joss concluded that the possible primary sources of a metastatic malignant lesion of the axillary nodes are (1) a small primary focus in the breast, (2) carcinoma of the tail of the breast, extending into the axilla, (3) carcinoma in accessory axillary breast tissue, (4) small nonpigmented melanoma, and (5) tumors of the lung and pleura.

No definite information could be found in the literature as to the relative frequency with which "occult" carcinoma of the breast and other "occult" primary tumors were associated with metastatic carcinoma of axillary nodes.

An understanding of the problem would be incomplete without the realization that a primary focus of carcinoma may not be found in the removed breast. The frequency with which this may be expected to occur is unknown. A search through the case records at the Mayo Clinic for the period 1907 to 1952 revealed 10 such cases. In each of these cases there was a preoperative microscopic diagnosis of metastatic carcinoma to an axillary node without evidence of a primary source, clinical examination of the breasts giving negative results. Subsequent radical mastectomy was performed and the breast was examined but pathologic study failed to reveal evidence of carcinoma. The subsequent course of the disease in these cases is unknown. Seven patients were still living when last heard from, and no further knowledge of a primary source was ascertained. Three patients have died without further information as to the site of the primary carcinoma.

The gross appearance of the lesions of the breast was of great interest. When it is realized that the size of these lesions ranged downward from a diameter of less than 2 centimeters to a diameter of only microscopic dimensions, it is readily understandable why they were "occult." In 3 cases the lesion was discovered only after repeated microscopic examinations. Fibrous mastitis producing generalized thickening of the breast was found in 7 cases and surely hindered the discovery of such small lesions. The position of the lesions, deep within the breast tissue, and the fact that a large percentage were of the comedocarcinoma type further hindered palpation of the lesions.

The presence of an inflammatory reaction surrounding the tumor, as was found in 28 per cent of cases in this study, had been noted by MacCarty, Haagensen, and others. Authors do not agree as to its influence on the cancer but a thesis by Eckstam, in 1949, indicated that it is a prognostic factor. He concluded that its presence gave a better prognosis. No conclusion regarding prognosis could be drawn from our study, since only 3 of the 7 patients concerned were treated more than 5 years ago and all 3 had subsequently died, 2 definitely from their carcinoma.

The outstanding feature in this study was the complete lack of signs and symptoms pointing to the existence of a primary cancer in the breast. The presence of an axillary tumor with or without symptoms referable to the breast, therefore, should cause the patient to seek medical care. Eighty-eight per cent of patients in this study appeared because of the presence of an axillary tumor. It is only at this point that the diagnosis can be established and treatment instituted, admittedly late in the course of the disease however small the primary lesion.

How long a lesion in the breast may remain before it can be recognized clinically is unknown, but evidence such as calcification as described by Shore and as seen in our series tends to indicate that considerable time can elapse. The presence of palpable axillary nodes of years' duration as described by Halsted and others including Cameron and as seen in our group of patients (3 of 25 patients had noted the presence of axillary tumors for more than 2 years) also illustrates the slow rate of growth of the primary lesion even when associated with early metastatic spread.

The recommendations for treatment of occult carcinoma of the breast are dependent upon the knowledge that there often exists within the homolateral breast a lesion of such small size that its detection is clinically impossible. Definite enlargement of the axillary nodes is an indication for biopsy. With definite information of metastatic adenocarcinoma to the axillary glands, it is imperative that the primary source be searched for. As we have already pointed out, no specific information is available as to what proportion of these patients will be found to have a primary focus in the breast. The breast, however, should be considered the most likely source, especially in women. A thorough search for other metastatic foci should be made, and if no focus is found and if no further evidence of spread exists, the treatment indicated is the same as for any carcinoma of the breast with axillary nodal metastasis, namely radical mastectomy.

The prognosis of occult carcinoma of the breast with axillary nodal metastasis should correlate with that of all carcinoma of the breast with axillary nodal metastasis. According to Harrington (11), the 5 year survival rate for patients who have carcinoma of the breast with axillary nodal metastasis is 32.5 per cent and the 10 year survival rate is 18 per cent. Percentages mean little, however, when they are based on as few patients as were included in our study. Nevertheless, it is of interest that 9 of 18 patients lived 5 years or more, and 6 of 12 patients lived 10 years or more after operation. This would seem to indicate a better prognosis than is observed for the average carcinoma of the breast with nodal metastasis. No explanation except possibly the high incidence of comedocarcinoma, the inflammatory reaction, and the small number of patients can be given for this finding.

SUMMARY

Data on 25 cases of occult carcinoma of the breast were studied to determine whether these differed from cases of mammary carcinoma in general. The term "occult" is used herein to refer to carcinoma of the breast that is manifest clinically on the sole basis of enlargement of the axillary nodes.

The occurrence of this condition was found to be rare. The age and sex distribution agreed with that of carcinoma of the breast in general. The diameter of the lesions in the breast was less than 2 centimeters in all cases, and less than 1 centimeter in 60 per cent of cases. A large percentage of the lesions were of the comedo type, and a significant number demonstrated the so-called inflammatory reaction about the tumor. Ninety-three per cent of the tumors were of grade 3 and grade 4 malignancy, but the prognosis was good as compared to that for carcinoma of the breast in general with nodal involvement.

This entity has been recognized and treated for many years, and the results of this study indicate the need of keeping this unusual possibility in mind.

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VENOUS THROMBOSIS, NECROSIS, AND NEOPLASIA

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THE appearance of an apparently spontaneous peripheral venous thrombosis, often multiple and migrating, should present the physician with a diagnostic problem that extends beyond the extremities. Peripheral venous thrombosis following a surgical procedure, parturition, prolonged bed rest, and infectious disease is commonly recognized. Thrombosis associated with trauma or infection about the lower extremities and with varicosities is not uncommon. The recognition of venous thrombosis as one of the clinical manifestations of thromboangiitis obliterans and the diagnosis of idiopathic migratory polyphlebitis are usually made without undue difficulty. We have seen in the past few years, 8 patients admitted to the hospital with symptoms and signs of peripheral venous thrombosis and/or pulmonary embolism. Seven had occult neoplastic lesions and 1 patient had tuberculosis.

The association of venous thrombosis and neoplasia is recognized only infrequently and for this reason it was felt worth while to present the following case histories and discussion. Many patients have been seen with spontaneous venous thrombosis in whom we were unable to find any associated lesion, but the occurrence of neoplastic lesions in the reported cases has prompted us to encourage a diligent examination of all viscera when a patient presents himself with venous thrombi of undetermined origin.

CASE REPORTS

CASE 1. G.I., a 27 year old female, was referred to University Hospitals because of anemia and phlebitis. She was in good health until some 7 months previous, when she began to notice easy fatigability, palpitations, dizziness, and exertional dyspnea. Four months before admission she developed pain in the right calf with tenderness, but no swelling or redness. A local physician was consulted and she was informed that she had phlebitis and anemia. Penicillin and several injections of vitamin B_{12} were given without any great response. She remained in bed for approximately 1 month after which time the pain had returned in the lower leg. Two weeks before admission she noticed difficulty in walking because of leg pain and noted that she had a daily fever. One week prior to admission, she developed redness, swelling, and pain in the right antecubital fossa and noted paresthesias in all extremities. There was a weight loss of 27 pounds in 6 months. Past history and systems review were entirely negative.

Physical examination revealed a temperature of 37 degrees C., pulse 120, respiration 22, and blood pressure 115/60. The patient was a thin, white female who appeared to be chronically ill. Positive physical findings were confined to the abdomen and extremities. Examination of the abdomen revealed that it was scaphoid without spasm or tenderness. The liver could be palpated 2 fingerbreadths below the right costal margin with a soft, smooth edge. There was a questionable mass in the right lower quadrant. Examination of the right arm revealed that the antecubital vein had a hard thrombus 6 inches long with marked tenderness on pressure. There was no redness or swelling over the region of the vein. Examination of the lower extremities revealed a positive Homans' sign bilaterally, and both calves were tender to pressure. Along the course of the left greater saphenous vein, there was tenderness. A painful firm nodule was palpated in the left midthigh. There were no color changes or edema. Laboratory findings revealed the urine to be normal. Hemoglobin was 8 grams, red blood count 3.48 million, white blood count 10,900, hematocrit 28, differentials—segmented neutrophils 71 per cent, lymphocytes 13, mononuclears 3, eosinophiles 4, basophils 9, and atypical lymphocytes 9. Prothrombin content was 63.5 per cent, blood urea nitrogen 6.8 milligrams per 100 cubic centimeters, serum protein 7.1 grams per 100 cubic centimeters, albumin 3.7, globulin 3.4 grams per 100 cubic centimeters. Bilirubin, cholesterol, and alkaline phosphatase were within normal limits. Stool examination was guaiac positive. Complete hematologic examination revealed hyperchromic microcytic anemia. Gastric analysis revealed no free hydrochloric acid in the fasting sample; however in the 1 hour sample there were 60 units of hydrochloric acid, 80 units total. Rumpel-Leede's test revealed no petechiae; the bleeding time was 4 minutes and 15 seconds, clotting time 7 minutes and 15 seconds with good clot retraction. Electrocardiogram was normal; chest films revealed a small area of increased density in the left midlung field. Bone

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survey was negative. Intravenous pyelograms were negative. The stools continued to be guaiac positive and a barium enema revealed a constricting lesion in the right colon. She was transferred to the surgical service and was prepared with multiple transfusions and sulfasuxidine.

On the thirteenth hospital day, a lapatotomy was performed. A circular lesion in the ascending colon 10 centimeters above the ileocecal valve was found. There was no evidence of obstruction at that time. Palpation of the liver revealed marked involvement of the entire liver by an infiltrative malignant tumor. Plaques of tumor occupied the entire apex of the liver as well as the underlying surface. A biopsy was taken from a lesion in the leading edge of the right lobe. No further procedure was done and the abdomen was closed. Postoperatively the patient ran a septic fever throughout her hospital stay. She was placed in an oxygen tent and put on penicillin and streptomycin with some improvement. She improved gradually, was ambulated, and was discharged on her seventh postoperative day. Pathologic examination of the liver biopsy revealed partially differentiated mucinous adenocarcinoma.

CASE 2. M.K., a 59 year old white female, was admitted to the medical service of University Hospitals with the chief complaint of a sore leg of 9 days' duration. She had had varicose veins for many years, with a left saphenous ligation being done in 1942. The varices of both legs have been repeatedly injected with sclerosing solutions. She had a large ulcer on the left leg and until the present illness had little trouble with the right. Five days prior to admission she awoke with a cramp in the right leg, followed by intermittent pain which became worse with motion. The leg became swollen, red, tender, and warm. She went to bed and remained there for 3 days. There was no chest pain, dyspnea, or hemoptysis. She had had a similar bout of inflammation of the leg 18 years before but none since that time. She had had an appendectomy in 1943.

Physical examination revealed a temperature of 38.7 degrees C., pulse 90, respiration 18, and blood pressure 180/90. The patient was short, well developed, and obese not appearing acutely ill. The abdomen was obese and soft. She had a right lower rectus scar and a small umbilical hernia. Pelvic examination disclosed a urethrocele. Rectal examination was negative. She had large varicosities of the left leg, hyperpigmentation over the left calf and ankle, and marked swelling of the right lower leg and foot with erythema, heat, and tenderness. There were calf tenderness and a positive Homans' sign on the right. There were good femoral and dorsalis pedis pulses bilaterally. On admission laboratory findings showed the urine to contain 15 to 25 white blood cells per high power field. Blood urea nitrogen was 9.8 milligrams per 100 cubic centimeters, hemoglobin 70 per cent, red blood count 4.96 million, white blood count 10,800, prothrombin content 98 per cent, and clotting time 8 minutes. The patient was treated with heparin, dicumarol, rest, and elevation. Prothrombin level remained below 30 for most of her hospital stay, and she was discharged improved on the eighteenth hospital day. Following her discharge for thrombophlebitis from the medical service, she was seen in the surgical outpatient department where a mass about 6 by 8 centimeters in size was noted in the right lower quadrant. She was referred to the gynecologic service for evaluation. Barium enema revealed what was thought to be an extrinsic mass on the cecum. A diagnosis of ovarian tumor was made.

She was readmitted 6 weeks later on the gynecologic service with a complaint of pain in the right lower quadrant for about 1 year. One year prior to admission the patient had noticed a cramping pain in the right lower quadrant which was intermittent, worse in the evening, but unrelated to eating or exercise. In the past year, the patient's bowel movements had been irregular, with alternating diarrhea and constipation. She noticed some bloody stools and lost about 10 pounds. Physical examination revealed relatively little change from the previous admission, except that at this time there was no edema of the extremities. Pelvic examination revealed a relaxed outlet as well as large cystocele and rectocele. An abdominal mass was palpated and found to be tender. This appeared to be an ill defined, tender, oval mass about 10 centimeters in diameter in the right lower quadrant which seemed to extend into the pelvis. Laboratory findings showed the urine to be normal. On admission the hemoglobin was 60 per cent, red blood count 3.5 million, and white blood count 8,000. Prothrombin time was 47 per cent of normal. At surgery a carcinomatous mass was found to involve the cecum and terminal ileum. Resection of the terminal ileum and cecum was done with an end-to-side ileocecostomy. It was noted at operation that the peritoneum was studded with carcinoma, as was the omentum. Pathologic examination revealed a dermoid cyst of the right ovary; partially differentiated mucinous adenocarcinoma of the cecum. Four days following discharge she developed swelling and tenderness of the right leg. She was readmitted, treated with bedrest, local heat, and elevation after which she improved rapidly, and was discharged on the ninth hospital day.

Cases 1 and 2 represent rather classic instances of right colon carcinoma with moderate anemias which were disregarded by the physicians in charge. All attention and treatment were focused on the peripheral venous thrombosis with little or no regard to the associated systemic disease. In Case 1, with a 7 months' history of symptoms of anemia and a 4 months' history of phlebitis, valuable time was lost which might have altered the fatal outcome.

CASE 3. P.B., a 46 year old single white woman, developed a sudden stabbing pain in the right side of her chest 11 days before entry. She was told by the physician who saw her 2 days later that she had pleurisy and possible pneumonia. She was started on penicillin. The pain cleared up and the patient was relatively asymptomatic until 2 days before entry, when she coughed up some dark blood. On the night of this day, she developed sudden pain in the left chest which persisted until entry. The patient noticed an enlargement of her lower abdomen of 3 months' duration.

Physical examination disclosed a temperature of 37.8 degrees C., pulse 90, respiration 22, and blood pressure 138/90. The patient was well developed and well nourished not appearing acutely ill. Examination at both bases of the lungs revealed dullness with the presence of medium crackling rales at the right base. Examination of the abdomen revealed a large mass in the lower abdomen extending to just above the umbilicus. Pelvic and rectal examination revealed a normal cervix and verified the presence of a smooth, large firm lower abdominal mass which could not be differentiated from the uterus. Laboratory findings revealed the urine to be normal. Hemoglobin was 75 per cent, red blood count 4.1 million, and white blood count 10,085. The serology study was negative. Blood culture was also negative. Mouse inoculation with sputum was negative for pneumococci. No acid-fast bacilli were found in the sputum smear. Admission roentgenograms of the chest revealed probable pneumonia in both lung bases with the chief manifestation being a transverse band of atelectasis with probable pleural thickening on the right. An admission electrocardiogram showed sinus tachycardia.

The patient's temperature ranged between 38 and 38.6 degrees C. throughout the first 9 hospital days despite penicillin. At gynecologic consultation a diagnosis of a fibroid uterus was made. On the eighth hospital day the patient noticed a swelling of the left leg and was seen to have moderate edema of this extremity without evidence of pain, inflammation, or loss of pulses. Upon surgical consultation at this time the diagnosis was iliac vein thrombosis, left, with question of abdominal neoplasm with extension into the iliac vein as a possible consideration. The patient was placed on heparin and dicumarol. Temperature gradually declined and except for 1 episode of hemoptysis, there was no recrudescence of symptoms. Roentgenograms of the twenty-second hospital day revealed a healing infarct in the left lung, atelectasis in the right lung base (segmental), probably secondary to pulmonary emboli. The patient was made ambulatory before discontinuing dicumarol therapy and had persistent edema of the left leg during this time, for which an elastic bandage was used with little benefit. She was discharged to be readmitted at a later date for investigation and removal of the uterine tumor.

She was readmitted on March 5, 1948 with a 3 day history of pain in the right popliteal area. Two days previous to admission, she noticed some swelling of the right leg. She did not notice chills, fever, or local heat. Physical examination revealed a temperature of 37.6 degrees C., pulse 100, respiration 18, and blood pressure 136/90. The patient did not appear acutely ill and her physical examination was essentially unchanged, except for 1+ pitting edema of both lower legs and moderate tenderness in the right popliteal space. X-ray examination revealed pulmonary fibrosis in the base of the left lung due to a healed pulmonary infarct. The patient was started on dicumarol and on the seventh hospital day she was taken to surgery where an exploratory laparotomy was performed. A large globular tumor which was a soft "necrotic" myoma was found. Hysterectomy was performed. The patient's postoperative course was uneventful and she was discharged on the tenth postoperative day, improved.

CASE 4. S.D., a 42 year old white male physician, was admitted to the hospital with the chief complaint of cough and chest pain of 6 weeks' duration. The patient was in good health until 6 weeks prior to admission at which time he contracted an upper respiratory infection. Shortly thereafter he noted a dull aching pain in the right heel which persisted for several days and was not associated with color changes or swelling. Two weeks later he developed a dry, and unproductive cough which became productive with sputum mixed with blood for 4 days prior to admission. Two weeks before admission he developed pain along the right costal margin, referred to the right shoulder, and had similar pain in the left chest and shoulder. One week prior to admission, the patient had a white blood count of 18,000. There was moderate temperature elevation without chills. With exertion and coughing, the chest pain became aggravated and he began to have shortness of breath. He noted no cyanosis or ankle edema. Four days prior to admission he was placed on penicillin. He admitted losing 10 pounds in weight. Past history was noncontributory. Physical examination revealed a fairly well developed, well nourished white male, acutely ill and with moderate respiratory distress. Blood pressure was 140/80, pulse 80, and respiration 18. Positive physical findings were limited to the cardiorespiratory system. Chest was symmetrical with slight limitation of extension bilaterally with tenderness over the right costal margin in the posterior axillary line. There was a slight diminution of breath sounds over the right lower lung and a few moist rales at the right base. There was no friction rub heard. The remainder of the physical examination was not contributory. Hemogram revealed moderate anemia with a white blood count of 12,350.

Roentgenograms 2 days following admission showed a recent pneumonic infarct at the left base. The patient was begun on penicillin. The cough and pain were persistent. Chest consultation was obtained which confirmed the impression of acute pulmonary infection with consolidation of the left lobe and pleural reaction, thought to be atypical pneumonia.

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The patient continued to cough and bring up small amounts of bright red blood. On the fourth hospital day, the patient developed pain and tenderness along the left brachial vein and slight calf tenderness on the left. Heparin and dicumarol were started. Clinical impression at this time was migratory thrombophlebitis with pulmonary infarct. Three weeks following admission the patient had a large pulmonary infarct and was in extremis with marked cyanosis which gradually improved over a period of 1 hour. Surgical consultation was obtained with regard to the possibility of inferior vena cava ligation. This was considered and deemed inadvisable. Four weeks following admission, 2 mobile, moderately tender, subcutaneous nodes were felt in the lower left side of the neck. These were removed surgically under local anesthesia. Pathologic examination of the nodes revealed anaplastic carcinoma simplex. Subsequent roentgenograms of the chest revealed a prominence in the region of the left hilum and evidence of bilateral pleuritis was noted. The patient's course fluctuated with periods of improvement followed by periods of marked dyspnea requiring oxygen therapy and episodes of thrombophlebitis in the arms and legs, despite anticoagulant therapy. The patient became confused much of the time, requiring large amounts of sedation. He quietly expired 4 weeks following admission. Autopsy revealed anaplastic adenocarcinoma of the lung which arose in the posterior branch of the left lower lobe. There were numerous metastases in the lung with extensive necrosis present. There was generalized thrombophlebitis particularly of the veins of the pelvis, arms, lungs, and prostate.

The patients in Cases 3 and 4 were admitted to the hospital because of pulmonary emboli. It is worthy of note that in Case 3, P.B., clinical evidence of venous thrombosis of an extremity was not noted until the eighth hospital day. At laparotomy, a large uterine myoma was removed which was centrally soft and "necrotic."

In patient S.D., Case 4, obscure aching pain in the right heel was followed by pulmonary emboli. Subsequent to his admission, he developed many thrombi in his arms and legs in spite of adequate anticoagulant therapy. Fisher, Hochberg, and Wilensky reported 4 cases of carcinoma of the lung in which there was thrombophlebitis antedating the identification of the lesion. They stress that when adequate anticoagulant therapy does not prevent further thromboembolic phenomena, a cancer should be suspected.

CASE 5. H.J., a 50 year old white male, was well until 4 months before admission when he noticed a rather sudden onset of cramping abdominal pain. This had been present most of the time since the pain characteristically was worse about 1½ hours after breakfast. The pain was also worse at night. There was slight relief with antacids. Pain was generalized over the lower abdomen. During the same period of time, the patient had been passing clots and strings of bright red blood intermittently. There was considerable relief from pain in the 6 weeks prior to admission after the patient was placed on a Sippy diet. There was no nausea or vomiting at any time. The weight loss was about 12 pounds. The patient had had some pain in the left arm for the past 4 weeks.

Physical examination revealed a temperature of 37.4 degrees C., pulse 86, and blood pressure of 124/76. The patient was a well developed and well nourished white male not appearing acutely ill. Positive physical findings were confined to the abdomen and extremities. There was slight tenderness in the epigastrium and the left upper quadrant of the abdomen. No organs or masses were palpable. Rectal examination was normal. There were 3 or 4 veins along the volar aspect of the left forearm which were thrombosed. Urine showed 1+ albumin; specific gravity 1.021, occasional white blood cell per high power field. Hemoglobin was 101 per cent; red blood count 5.16 million, white blood count 5,400; prothrombin was 97 per cent; blood urea nitrogen 14.3 milligrams per 100 cubic centimeters; serum proteins, 6.7 grams per 100 cubic centimeters.

On the patient's third hospital day, because of roentgenographic findings of prepyloric ulcer and questionable cancer the patient was taken to surgery for exploration. At exploration a carcinoma of the stomach with metastases to the liver was found. The pathologic diagnosis was partially differentiated papilliferous adenocarcinoma. The patient's postoperative course was uneventful and he was discharged on the eighth postoperative day.

The patient was readmitted 4 weeks later because of phlebitis of both lower extremities. Since discharge the patient had some pain along the anterior aspect of the left leg below the knee, which was treated by rest, elevation, and heat. The pain became steadily worse until the patient could not walk and finally the right leg became similarly affected, but not quite so severely. Physical examination on admission was essentially as before. The superficial veins of both lower extremities were cord-like and there was pain on palpation along the left tibia anteriorly. The skin was warm and dry. There was no calf tenderness. Homans' sign was not present.

On the night of admission, the patient noticed an onset of pain in the left chest posteriorly, which was made worse by inspirations, and this was associated with fever and a friction rub was heard over the left chest posteriorly. A diagnosis of pulmonary embolism with infarction was made. He was treated with heparin and dicumarol. On the seventeenth hospital day he began to have severe gastrointestinal hemorrhage and he died on the twenty-second hospital day. No autopsy was obtained.

The patient of Case 5 with carcinoma of the stomach had gastrointestinal symptoms for 4 months prior to admission. One month before admission he developed pain in the left arm. Several thrombosed veins were identified in the physical examination. There was no evidence of acute phlebitis present at that time nor was there any history suggestive of phlebitis. At operation, liver metastases were found, indicating a lesion of moderate duration. The findings of thromboses should have alerted everyone to the probable presence of neoplastic disease.

CASE 6. This was the second University Hospitals admission of F.C., a 40 year old housewife complaining of pain, swelling, and fever of both legs of 3 weeks' duration. The patient had a severe attack of influenza necessitating 2 weeks' bed rest at home, 5 weeks before admission. Two years previously she had noticed a decrease in menstrual flow to 1 day every 32 days, with associated severe back pain, headache, faintness, abdominal cramps and lower abdominal fullness, increasing gradually to date despite hormone therapy. Three weeks before admission, following modified bed rest for influenza, she noticed swelling and pain in the right ankle with red streaks going up the inner side of the leg to the knee for the next 2 days. Pain, swelling, and redness then shifted to the left ankle, progressed rapidly to the thigh, and she noticed a golf-ball sized red, hot, tender mass in the left groin for 2 weeks thereafter. The right leg improved except for a small, red, tender knot in the right calf which persisted to date. The left leg became more and more swollen, venous distention occurred, she developed pain in the hip until she was unable to walk, which was 3 days before admission. She had noticed headache, chills, and fever for the 3 days prior to admission.

Physical examination revealed a temperature of 38.5 degrees C., pulse 88, respiration 22, and blood pressure 120/90. The patient was a well developed, well nourished female who was acutely ill, complaining of swelling and pain in the left leg. The abdomen was symmetrical, but there was a fullness below the umbilicus. Liver, spleen, and kidneys were not palpable. There was a large 15 centimeter firm, nontender, movable mass filling both lower quadrants, apparently confluent with the uterus. The arms were normal except for a 2 centimeter tense round swelling of the volar aspect of the wrist beneath the palmaris longus. Examination of the legs revealed that there was right venous distention and tortuosity which was moderate and 1+ ankle edema. There was a small 2 centimeter firm, tender, red area in the middle third of the right calf on the medial aspect. There was no tenderness on the thigh or groin. Examination of the left leg revealed marked enlargement with distention and tortuosity of superficial varicose veins, 3+ ankle edema. There was induration and local heat and tenderness over the entire calf, thigh, and groin, with a hard induration, and the varicosities were most marked on the posterior calf. Peripheral arteries were normal. Pelvic examination revealed a moderately relaxed outlet with a moderate rectocele. The cervix was slightly lacerated. The uterus was indistinguishable from a large firm mass filling the lower abdomen. Laboratory findings revealed the urine to be normal; prothrombin level 67.5 per cent of normal; hemoglobin 75 per cent; red blood count 3.95 million; and white blood count 76,000.

The patient was treated with heparin and dicumarol. Her temperature was down to normal on the fifth hospital day. She was readmitted 3 weeks later for abdominal laparotomy. On the first hospital day, she was taken to surgery where an abdominal exploration was done. The lower abdomen was found to be filled with a dense cystic mass which measured approximately 20 centimeters in diameter. An incision was made in the cyst wall and the contents were drained out by suction. About 1 gallon of fluid was obtained. The adherent viscera were then completely separated from the sac, which was removed, along with the right tube and ovary. The uterus was found to be small, anterior in position, and normal in appearance. The left ovary was prolapsed into the cul-de-sac and attached to it was a papillary growth which had the appearance of a carcinoma. A supracervical hysterectomy and left salpingo-oophorectomy were done in the usual manner. Pathologic diagnosis disclosed serous cystadenocarcinoma of the ovary.

CASE 7. A 42 year old colored female, with a chief complaint of pain in the left leg, dated the onset of her illness 10 days prior to admission when she awoke in the morning with severe sharp pain in the left leg, beginning in the left hip, and radiating down the posterior aspect of the leg to the ankle. The pain disappeared following what she called "hip exercises" and she went to work. The following morning she suddenly became dizzy and fell. This was followed by an immediate recurrence of the pain which continued. This pain was accentuated by activity, coughing, and sneezing, and was accompanied by a "pins-and-needles" sensation in the leg.

Physical examination showed her temperature to be 37.2 degrees C., pulse 68, respiration 20, and blood pressure 120/80. The patient was well developed and well nourished complaining of moderate pain in the left leg. Filling the hypogastrium was a large, very firm, nontender, regular, fairly well defined mass extending from the symphysis to the umbilicus. In the left lower quadrant was a discrete nodule which was apparently attached to the aforementioned mass. The extremities were essentially normal, except for hyperesthesia of the left leg up to the fourth lumbar dermatome. Bilateral straight leg raising revealed pain in the left leg when the hips were flexed at a 45 degree angle. Achilles' reflex was absent on the left. Pelvic examination by a gyne-

cologic consultant revealed that the cervix was firm, freely movable, and nontender. The uterus was enlarged to approximately 5 times normal size by multiple myomas. Laboratory findings revealed the urine to be normal. The hemoglobin was 12 grams, white blood count 7,600, serology negative. The patient was placed in Buck's traction and relief of pain was obtained. Roentgenograms of the lumbosacral spine showed scoliosis of the lumbar spine with slight narrowing of the interspace between the fourth and fifth lumbar vertebra. On the twelfth hospital day, the patient noticed that the left leg above the level of the traction straps appeared swollen. There was also an onset of twisting pain in the calf of the left leg the night previous. She was seen by one of us (W.D.H.) who noted the development of a spontaneous venous thrombosis in the presence of a hard nodular pelvic mass and rather rapid development of backache. He suggested the possibility of a neoplasm with vertebral metastases, and recommended heparin and dicumarol for the thrombosis. Prothrombin time was kept at a low therapeutic level. Calf tenderness decreased markedly and on the seventeenth hospital day, because the patient continued to complain of a moderate amount of leg pain and tenderness, a left lumbar sympathetic block was done with questionable effect. She improved steadily and was discharged with only a slight amount of edema of the left leg.

She was readmitted 2 months later for elective hysterectomy. Panhysterectomy and appendectomy were done without difficulty. The uterus measured 32 by 12 by 8 centimeters and weighed 800 grams. Its contour was distorted by numerous nodular masses measuring from 0.5 to 8 centimeters in diameter. Her postoperative course was uncomplicated.

Cases 6 and 7 illustrate similar histories of antecedent peripheral thromboses and neoplasma, in one carcinoma of the ovary and in the other uterine myomas. In both cases, the size of the pelvic tumors was considerable, and although it cannot be denied that there was probably some increase in peripheral venous pressure it was the appearance of the thrombosis that led these patients to seek medical attention.

CASE 8. M.K., a 61 year old white male, was admitted with the chief complaint of pain and swelling in the left leg. Three weeks before admission, the patient developed pain in his left heel, followed by gradual progressive pain in the left leg. At first he thought the pain was due to an ill-fitting shoe and was given orders by his plant physician to stay off his feet as much as possible. In spite of these suggestions, the pain, tenderness, and swelling persisted, and on admission he stated that the foot and ankle swelled to about half again the size of the right one. He denied any fever, chest pain, chills, and cough. His past history was essentially negative.

Physical examination revealed a temperature of 27.7 degrees C., pulse 76, respiration 24, and blood pressure 130/80. The patient was a stocky, well nourished male. Physical findings were confined to the left leg and prostate. Examination of the left leg revealed slight pain and tenderness on palpation over the left heel and calf. There was no change in skin temperature and there was no visible swelling, edema, or erythema. Neurologic examination was negative. Prostate was of normal size; there was induration along the right lateral border but there appeared to be no extension beyond the capsule of the gland. A diagnosis was made of subsiding deep venous thrombosis. Laboratory findings revealed that the urine was negative except for an occasional white blood cell per high power field; serum proteins 6.4 grams per 100 cubic centimeters; cephalin flocculation 3+; serum alkaline phosphatase 4.8 Bodanski units; serum acid phosphatase 8.9 units. Hemoglobin was 107 per cent; red blood count 5.55 million, white blood count 5.550; prothrombin 100 per cent. Barium enema revealed a roentgenographically normal colon, and films of the spine showed deforming spondylosis and hypertrophic arthritic changes of the spine and pelvis.

The patient was started on dicumarol and scheduled for orchiectomy but he refused and was discharged. He was given 3 milligrams of stilbestrol daily, and 1 month later he was readmitted to the hospital for bilateral orchiectomy. Physical examination on this admission revealed that his condition was unchanged. On the patient's fourth hospital day he was taken to surgery where a bilateral orchiectomy was done. The postoperative course was uneventful. Chest film at that time showed probable fibrotic tuberculosis of the left apex but there was no conclusive evidence of metastatic involvement of the lumbar spine, pelvis, or chest. He was discharged, improved, on the seventh hospital day.

He was readmitted to the hospital 5 months later because of chills and fever of 6 days' duration. On his discharge from the last hospital admission he was given 3 milligrams of stilbestrol, which was later decreased to 1 milligram daily. His leg pain continued and a mass was palpated in the left gastrocnemius. This was excised and a pathologic diagnosis of nonspecific granuloma was made, although tuberculosis was suspected. Since the orchiectomy his general health had deteriorated. Six days before this last admission he developed severe frontal and occipital headache. Five days before admission he had a series of mild chills and malaise. The headaches increased in severity, he became somewhat disoriented, and was seen by a private physician who started him on penicillin.

Physical examination revealed a temperature of 38.6 degrees C., pulse 50, respiration 20, blood pressure 140/76. The patient appeared to be confused mentally and responded sluggishly to questioning. The liver was palpated 2 fingerbreadths beneath the costal margin on deep inspiration. Examination of

the prostate revealed that the right lobe of the prostate was markedly enlarged and firm. The left lobe was indurated and moderately enlarged. Urine showed 1+ albumin, occasional white blood cells per high power field. Hemoglobin was 83 per cent; red blood count 5.5 million; white blood count 7,200. A lumbar puncture was done on the first hospital day. Cell count was 115 per cubic millimeter, all monocytes. The Pandy test was positive. Ross-Jones test was weakly positive. Protein was 350 milligrams per 100 cubic centimeters; Wassermann test was negative. Dynamics: 210/120; normal. Spinal fluid on direct smear showed no acid-fast bacilli and gram stain showed no organisms.

The hospital course of the patient was markedly febrile, and he became comatose with twitching of the right arm. There were marked Cheyne-Stokes respirations and moderate nuchal rigidity. He died on the seventh hospital day. Autopsy diagnosis was tuberculosis of the prostate and both adrenals with tuberculous meningitis.

The last case is the only one we have seen in which a chronic infectious disease was associated with thrombosis. The elevation of the serum acid phosphatase combined with the physical examination of the prostate led to the error in the diagnosis of the prostatic lesion.

Barker observed that when the thrombophlebitis complicated infectious diseases such as typhoid and pneumonia it occurred relatively late in the disease and usually involved large vessels such as the femoral or iliac veins. In other more acute diseases such as tonsillitis and appendicitis, the greater saphenous system was involved. In 91 cases complicating the infectious diseases, the veins of the legs were involved in all patients. The veins of the arms were diseased in 3 patients.

Miller and associates, in their study of carcinoma of the pancreas, found that there appeared to be a direct relationship between venous thrombosis and the grade of malignancy. They found that venous thrombosis occurred in 12 per cent of grade I carcinomas and rose to 44 per cent in grade IV neoplasms. The iliofemoral veins were involved in 41 per cent of the cases, being second only to the portal vein (48 per cent).

DISCUSSION

Sproul, in 1938, called attention to the frequent association of multiple phlebothromboses with malignant tumors of the body and tail of the pancreas. In a series of 4,258 consecutive necropsies, a carcinoma was found to be associated with thrombosis of the veins of the neck, abdomen, pelvis, and extremities. The cases of the more common carcinomas were studied by Sproul, and the distribution of the venous thrombosis recorded. In 125 cases, 56.2 per cent of carcinomas in the body or tail of the pancreas, at least a single thrombus was present; in 31.3 per cent of these cases, widely disseminated venous thrombosis occurred. Inflammation or invasion of the vessels by tumor tissue could not be incriminated as a cause of thrombosis except in 1 case. Carcinoma arising in the head of the pancreas was associated with multiple thromboses in 9.7 per cent of the cases. Carcinoma of the stomach showed a high incidence of thrombus formation and in 2 cases were widely distributed.

Kenney, in 1943, reported a review of 9,800 autopsies, in which there were 30 cases of carcinoma of the head of the pancreas, and of these not 1 was associated with multiple venous thrombi. In 5 a single thrombosed vein showed invasion by tumor or could be explained readily by a well recognized mechanism. Twenty-one cases of carcinoma of the body or tail of the pancreas were found. Seven or 33.3 per cent showed multiple venous thrombi. Ten, or 47.6 per cent, had at least 1 thrombus.

Trousseau, circa 1868, was perhaps the first to point out that thrombophlebitis is not a sign belonging peculiarly to cancer of the stomach, but that it is equally symptomatic of cancer of other internal organs. It is of interest to note that Trousseau himself perished with carcinoma of the stomach, thrombophlebitis being the initial symptom. Others have called attention to various other visceral carcinoma in which peripheral phlebitis may be the presenting symptom.

Barker, in 1936, commenting on thrombophlebitis complicating infectious disease noted that the saphenous vein was involved in 91 cases and in 3 cases in addition arm involvement was present. In 58 noninfectious systemic diseases, neoplasia was incriminated in 34 cases. The thromboses associated with visceral carcinoma usually occur in the superficial

veins of the legs or forearms. They may be single or multiple as well as recurrent. In 6 of the 8 cases reported, the site of initial thrombosis was in the lower extremities, and in the arms in 2. Characteristic features of the thromboses were the appearance of thrombosis in most cases with little evidence of an inflammatory reaction. Similar findings were noted by Edwards and Cooper and Barker. In general, the differential diagnosis of peripheral phlebitis complicating carcinoma involves ruling out commonly known causes for thrombosis. The phlebitis of thromboangiitis obliterans is usually found in younger males who invariably use tobacco. The arterial involvement of Buerger's disease may or may not have taken place at the time of the examination. Edwards emphasizes the fact that the progress from one area, or one vein, to another, is not so rapid or so extensive as in carcinoma. With visceral neoplasias, patients are in the older age groups and progress is rapid. If months or years have elapsed between episodes of thrombosis, true idiopathic thrombophlebitis should be considered. The histologic picture of thromboangiitis obliterans is characteristic and biopsy will permit definite differentiation.

Pulmonary embolism as the initial finding appeared in 2 of our 8 cases. Indeed in patient S.D., with pulmonary emboli, definite thromboses were not noted until the fourth hospital day after which they progressed rapidly in spite of anticoagulant therapy.

The mechanism for the production of thrombosis remains obscure. The increased venous thrombosis accompanying carcinomas of the body and tail of the pancreas has been attributed to the release of trypsin into the systemic circulation secondary to the pancreatic duct obstruction or capillary damage. The role of trypsin appears yet to be clearly elucidated although it is well recognized that small amounts of trypsin in vivo will promote coagulation by the conversion of prothrombin to thrombin, whereas larger amounts produce shock with prolongation of the clotting time.

Lasher and McCabe produced experimental acute pancreatitis in dogs and measured a shortening of the clotting time. There was a progressive lengthening of the prothrombin time after the first few hours suggesting that the available prothrombin was being depleted. The coincident prolongation of the clotting time may be another indication of this, or may signify destruction of thrombin by the continued action of trypsin.

Rush and Cliffton reported an increased titer of serum proteolytic activity with experimental acute pancreatitis in dogs. Innerfield and co-workers refer to data that intravenous trypsin in large doses depresses levels of AC-globulin, prothrombin, antithrombin and fibrinogen in dogs. All returned to normal in a few hours except antithrombin. Using a plasma antithrombin test they studied 440 patients. They reported an elevated antithrombin titer in acute pancreatitis, exacerbations of chronic relapsing pancreatitis, pancreatic cysts and fibrocystic disease, and carcinomas of the head of the pancreas. In 5 proved cases of carcinoma of the body and tail of the pancreas in which we might expect more changes, the antithrombin levels were normal or low, perhaps indicating an increased tendency toward thrombosis. Shingleton and associates studied the use of a sensitized clotting test (paritol-C) combined with the use of secretin and urecoline and noted a change in blood coagulability in a significant number of patients with pancreatic carcinoma and chronic relapsing pancreatitis.

Admittedly, the associated enzymatic disorders in pancreatic disease may alter coagulability, the same mechanisms cannot be incriminated in neoplastic diseases of other organs, or in infectious diseases.

Moolten and associates, in a review article of the role of blood platelets in thromboembolism, noted increased platelet adhesiveness and thrombocythemia in surgical and accidental trauma, ischemic "necrosis" such as myocardial infarction, cutaneous irritation, and neoplasms. They emphasize that the determination of persistently high platelet adhesiveness may prove helpful in the differential diagnosis of suspected cancer in the absence of pathognomonic signs and in the early detection of occult cancer.

No one has demonstrated malignant infiltration of the vein wall with peripheral thrombosis. Admittedly, there may be local invasion at the tumor site, but the peripheral

thrombosis microscopically resembles the ordinary bland thrombosis of the recumbency state.

Since in the case of patient P.B. the soft necrotic myoma was complicated by the antecedent history of thrombosis, it occurred to us that the common denominator for peripheral venous thrombosis may be the presence of necrotizing tissue of either inflammatory or neoplastic origin. Miller's observation that the incidence of venous thrombosis increased directly with the grade of malignancy in carcinoma of the pancreas offers evidence along these lines, as it is well known that with increased growth of neoplasms the blood supply is often inadequate and necrosis of tumors is commonplace. Perhaps proteolytic enzymes are elevated in response to such a process, or there may be produced in necrotizing or neoplastic tissue, specific substances which alter coagulability. Lawrence and coworkers recently reported an experimental study demonstrating a thromboplastic property of the transplantable V_2 carcinoma in rabbits. It is here that we believe further investigation is necessary to ascertain the effects on the clotting mechanism of necrosis of tissue produced by thermal, chemical, irradiation, infectious, and neoplastic processes.

Edwards' thought-provoking question "Is the patient always doomed once the thrombophlebitis is detected?" is answered negatively by us. Vigorous diagnostic effort should be undertaken to determine the etiology of the thrombosis and the associated disease, and, when possible, neoplasms should be attacked in an effort to cure the patient as is done in cancer elsewhere. In many cases, the underlying disease may prove to be nonmalignant in character.

SUMMARY

1. We have presented the case histories of 8 patients admitted to the hospital with symptoms and signs of peripheral venous thrombosis and/or pulmonary embolism. In 7 of the 8 cases, an underlying neoplasm was discovered. In the remaining case, tuberculosis was the associated disease.

2. Attention is called to the fact that in the presence of necrotic tissue in tumors and inflammations the physiologic response of the host to necrosis may alter blood coagulation in some, as yet, undetermined manner.

3. Spontaneous peripheral venous thrombosis should alert the physician to the possibility of an obscure visceral neoplasm, and vigorous diagnostic effort should be undertaken to identify the site.

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THERMAL BURNS OF THE RESPIRATORY TRACT

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THERMAL injury of the respiratory tract has not received extensive recognition. It is uncommonly associated clinically with even extensive cutaneous burns which is rather surprising considering the exposure of the respiratory passageways to the intensive heat of the atmospheric gases associated with flame or explosion burns. The clinical manifestation of respiratory tract injury may follow noxious gas or smoke inhalation. Although it is unusual for the burned patient to be exposed to heat alone, thermal injury to the respiratory tract may occur and is associated with a high mortality. It was the purpose of these experiments to produce respiratory passageway and parenchymal pulmonary burns in the dog to determine the response of the injured tissue and, if possible, to find a satisfactory method of treatment.

The experimental production of a burn in the respiratory tract of the dog distal to the trachea by hot air alone is difficult to achieve. Moritz[1] demonstrated that air heated sufficiently to burn the skin can be inhaled without injuring the lungs. In his experiments the temperature of inhaled heated dry air rapidly dropped when passing through the larynx and trachea and did not produce thermal injury to the lower respiratory passages. Only after destructive burning of the proximal air passage had occurred did sufficient heat reach the lung to produce thermal injury.

Steam inhalation, however, can produce a burn in the lower respiratory passages and the more central portions of the lung parenchyma. This is not unexpected when the low heat capacity of dry air is compared to the heat capacity of water and the enormous latent heat energy of steam. It would require approximately 4 liters of air cooling 1 degree to release heat equivalent to that released by only 1 gram of water cooling 1 degree. More than 2,000 liters of air cooling 1 degree would be required to equal the heat released by the condensation of 1 gram of steam to 1 gram of water. For this reason, steam inhalation was thought to be the most suitable means of producing a burn of the respiratory tract in the dog.

In addition to producing thermal injury to the respiratory system it was desirable, in order to fulfill the particular requirements of this study, that the burn be of such severity as to give objective evidence of its presence, that it permit a survival time of sufficient duration so that the effect of the treatment could be evaluated, and that the burn could be reproduced with a sufficient accuracy that the result would be predictable in successive dogs. Furthermore, in anticipation of methods of treatment which were to be investigated, it was necessary that in some instances the dog's hematocrit be kept constant and that the dog be heparinized.

METHOD

Dogs were anesthetized with sodium pentobarbital administered intravenously. The average initial dose was 25 milligrams per kilogram body weight which was supplemented as required. An endotracheal tube was used to maintain an adequate airway, to provide a port of administration of steam distal to the larynx, and to permit sampling of tracheal fluid if present. The dog was heparinized if required, as in a portion of the experiments, and a cannula was placed in the femoral artery for blood pressure measurements and arterial sampling. A second cannula was placed in the femoral vein

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[1] MORITZ, ALLAN R. Symposium on Burns, National Academy of Science, National Research Council, Washington, D. C., 1951.

for the replacement of all blood drawn for sampling with an equivalent amount of donor blood and for the administration of a plasma substitute (dextran and gelatin) in those experiments in which the hematocrit was maintained near the preburn value. Preceding the burn an arterial blood specimen was taken for determination of free hemoglobin content of the plasma, plasma and whole blood specific gravity, whole blood hydrogen ion concentration, oxygen capacity, oxygen content, and carbon dioxide content. Similar determinations were made at frequent intervals following the burn.

The three methods used for burning the respiratory system with steam were: (1) voluntary inhalation of steam, (2) inhalation of steam when the phrenic nerves were stimulated electrically, and (3) steam inhalation while ventilation was controlled by a respirator. The progression to different methods was in anticipation of obtaining a reproducible burn as manifest by time of appearance of rales, edema, arterial blood desaturation, and uniform survival times.

The first series of 14 dogs were burned by directing steam at 100 degrees C. from an insulated portable autoclave through a short insulated connecting tube into the intratracheal tube. The dog inhaled the steam by voluntary inspiration, and there was free egress of steam and gases around the loosely fitting endotracheal tube with exhalation. A uniform exposure period of 1 minute was used in this group but the number of inhalations during the period varied from 9 to 34 and the volume of each respiration varied considerably. It was thought a more uniform method of exposure should be sought.

A second group of 6 dogs were burned by the following method: Insulated electrodes were placed in contact with both phrenic nerves exposed in the neck. Three solenoid valves were placed in the tubing from the steam generator to the endotracheal tube; one vented the steam generator to the atmosphere, one vented the endotracheal tube to the atmosphere, and the third opened or closed the tubing from the generator to the endotracheal tube (Fig. 1). As the current was passed to the electrodes in contact with

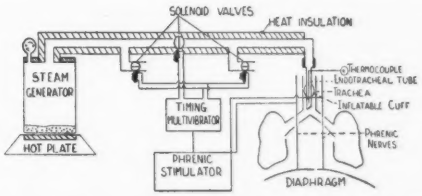

Fig. 1. Diagram of apparatus for producing uniform pulmonary burns with steam at atmospheric pressure showing the circuit used for simultaneous stimulation of the phrenic nerves and release of steam into intratracheal tube.

the phrenic nerves the tubing from the steam generator to the endotracheal tube was opened, the vents to the atmosphere were closed. When phrenic stimulation ceased the tubing from the generator to the endotracheal tube was closed, the vents to the atmosphere were opened. Preceding burning, the dog was hyperventilated until spontaneous respiratory movements ceased, then a predetermined number of maximal diaphragmatic contractions were produced by electrical stimulation of the phrenic nerves as the free inflow and egress of steam occurred. A trial period proved this method to have the disadvantages of requiring an additional operation; electrical stimulation occasionally failed to produce diaphragmatic contraction; dislodgment of electrodes occurred; and the respiratory movement produced resulted in extremely rapid diaphragmatic contractions not accompanied by movement of the chest wall. These disadvantages led to the trial of a third method in 8 dogs.

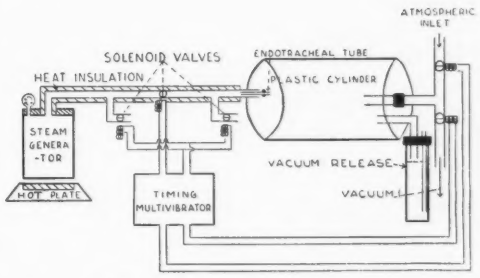

Fig. 2. Working diagram of respirator and steam generator.

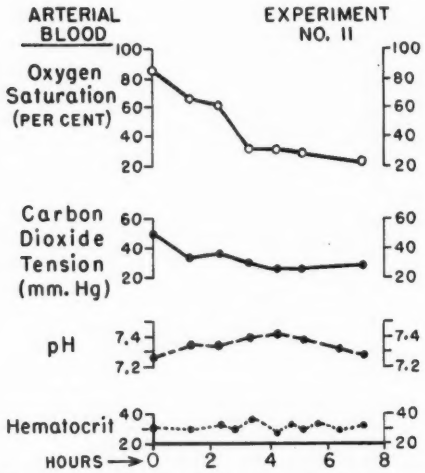

Fig. 3. Arterial blood findings in control following respiratory passage steam burn.

The dog was placed in a modified Drinker type respirator (Fig. 2). The endotracheal tube, previously placed within the trachea of the anesthetized dog, first communicated with the atmosphere through a seal in the cover of the respirator. Two solenoid valves, controlled by the same multivibrator used for the control of steam from the generator, alternately connected the respirator to a vacuum of approximately 29 centimeters of water and then to atmospheric pressure. The animal was noted to have very marked excursions of the chest and abdominal wall while in the functioning respirator. The ventilation was of sufficient degree that respiratory efforts ceased after approximately 2 minutes of ventilation by the respirator. Apnea of short duration occurred when ventilation was discontinued. The steam generator was then connected to the endotracheal tube during the apneic period and the respirator was again started. The solenoid in the vacuum line passing to the respirator opened, producing a maximum inspiration. This was synchronized with the solenoid valve admitting steam from the generator directly to the respiratory passage.

On expiration the previously mentioned solenoids closed and 3 other solenoids opened. One of these permitted the pressure within the respirator to become atmospheric, another permitted the escape of expired gas (expired air and condensed steam) from the respiratory passageway, and the third opened to the atmosphere to prevent an increase above atmospheric pressure within the steam generator while the steam was not being directed into the respiratory passageways.

A thermocouple was placed within the trachea just distal to the lower end of the intratracheal tube. The temperature was recorded at the time of the burning. The burn was given by 6 inspirations, each of 2.2 seconds' duration. Expiration was 3.8 seconds in duration. This method seemed to fulfill the requirements of respiratory control during administration of the steam.

After burning, continuous observations of systemic blood pressure and respiratory rates were made. Arterial blood samples were drawn at 1 to 2 minute intervals for a period of 6 minutes for determinations of free hemoglobin content. Arterial blood hydrogen ion concentration, oxygen capacity, oxygen content, carbon dioxide content, free hemoglobin content of the plasma, and plasma and whole blood specific gravity determinations were made intermittently until the dog died or recovered from the acute manifestations of the injury. An autopsy was performed upon all of the animals. The trachea was clamped before opening the thorax; the heart and lungs were removed intact and then weighed individually. Heart to lung weight and lung to body weight ratios were determined. Portions from vital organs were removed for histologic study.

RESULTS

The findings in the dogs of groups I and III were sufficiently consistent that some comparisons can be made. The findings in the individual dogs in group II varied to the extent that burns produced by this method could be of no use for the purpose of this study, and consequently this group of 6 dogs will be eliminated from consideration.

The findings following steam inhalation in both groups I and II were similar. Within 5 to 10 minutes after burning, rales could be heard over both lung fields. Within 30

minutes frothy fluid flowed from the endotracheal tube and continued until the death of the dog. A chart of arterial blood oxygen saturation, calculated carbon dioxide tension, hydrogen ion concentration, and hematocrit in the usual control experiment with plasma substitute is shown in Figure 3. Similar findings were present in those dogs which had no plasma replacement. The respiratory rate of the dogs with gross pulmonary edema showed no significant change in spite of the marked anoxia. Systemic blood pressure was maintained until shortly before death, at which time there was a rapid fall.

The significant autopsy findings were limited to the thorax. Total pleural fluid content varied from none to 350 cubic centimeters. There was a large accumulation of gelatinous fluid about the trachea and throughout the mediastinum. The trachea and bronchi were filled with large amounts of frothy pink fluid of approximately the plasma specific gravity. The average lung to body weight ratio of dogs dying following the burns were 0.0295. The normal ratio is 0.0125. Histologic changes are shown in Figure 4.

Fig. 4. Section of lung from burned dog. Abundant amount of fluid in alveoli.

SURVIVAL TIME

In calculating survival times, it was necessary to eliminate 1 dog in group I as the time of death was not known. The average survival time in group I with this exception was 5 hours and 47 minutes. In group III it was 6 hours and 39 minutes. The median in group I was 4 hours and 6 minutes, in group III, 4 hours and 11 minutes. Each group had 1 dog that received a low temperature burn. The intratracheal thermocouple in 1 instance recorded a temperature of 76 degrees C., in the other 90 degrees C. Both dogs survived for a period longer than 20 hours. If the only dog that survived over a period of 20 hours in each group is eliminated from the averages, the average survival time of group I is 4 hours and 16 minutes and in group III, 4 hours and 30 minutes. A comparison of survival times would indicate that burns comparable in severity were given by each of the two methods used.

PLASMA REPLACEMENT

The use of a plasma substitute to maintain the hematocrit near the preburn value did not greatly alter the survival time. In a group of 12 dogs the hematocrit was kept near the preburn value by the administration of an appropriate amount of a plasma substitute (dextran or gelatin). The quantities given varied from 233 to 1,750 cubic centimeters; the average was 840 cubic centimeters. The average survival time was 4 hours and 31 minutes, the median was 4 hours and 6 minutes. Nine dogs were not given a plasma substitute. The hematocrit always increased, the average rise was 25 points, the maximum rise 41 points, and in this instance the hematocrit increased to 78. The average survival time was 8 hours, the median was 4 hours and 37 minutes. Two dogs of this group which received low temperature burns survived a period of over 20

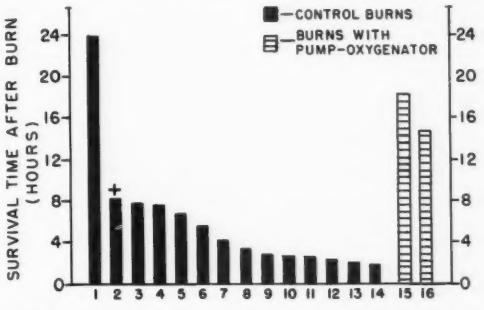

Fig. 5. Survival times after steam burn of respiratory tract in dogs with pulmonary edema treated by partial extracorporeal circulation compared to nontreated dogs.

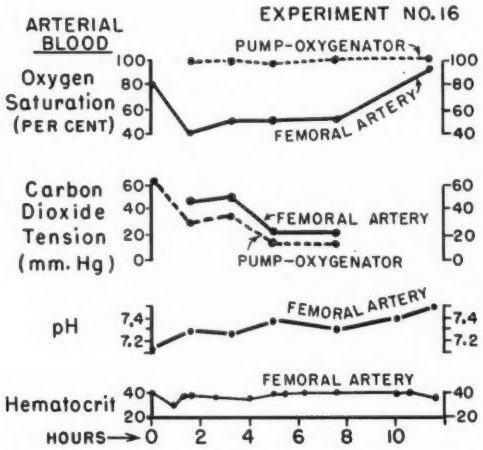

Fig. 6. Arterial blood findings usually present following respiratory passage steam burn and treatment with pump oxygenator.

hours. If these are eliminated the average survival time was 4 hours and 4 minutes and the median 3 hours and 31 minutes.

The dogs that received a plasma substitute had more severe edema of the lungs. The dogs that received a plasma substitute of sufficient quantity to maintain the hematocrit near the preburn value had an average lung weight to heart weight ratio of 3.5, a median of 3.3. Those which received no plasma substitute had an average ratio of 2.8, a median of 2.6. The average ratio of the weight of the lungs to the body weight of the dogs was 0.032 in the dogs receiving plasma substitute and 0.026 in the burned dogs not receiving a substitute.

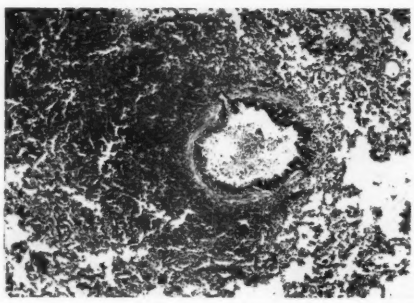

Fig. 7. Section of lung from burned dog subsequently treated with partial extracorporeal circulation. Extravasation of blood into alveoli prominent.

From data obtained the cause of death in all animals receiving respiratory tract burns was a progressive obstruction of the air passages with edema fluid. In 1 instance 1,025 cubic centimeters of plasma-like fluid was discharged from the trachea in a 5 hour and 40 minute period. There was progressive anoxia. In 17 experiments in which the required data are available the arterial blood was 80 per cent saturated preceding the burn. At an average time of 60 minutes following the burn it was 60 per cent saturated, and at an average time of 29 minutes preceding the death of the dog it was 25 per cent saturated. It was thought that better oxygenation of the blood could be obtained and carbon dioxide be eliminated by passing a portion of the circulating blood through an extracorporeal lung. This was done in 2 animals burned by the method described in group I. Only a partial extracorporeal circulation was established. Blood was continuously withdrawn from a peripheral systemic vein, passed through an extracorporeal lung, and reinjected into the right brachial or carotid artery. In each instance the flow rate through the extracorporeal circulation was 450 milliliters per minute or about 40 per cent of the estimated cardiac output of the animals. As the extracorporeal circuit had been filled with blood with a normal hematocrit it served as a buffer against change of the hematocrit of the experimental dog. The period of survival in these 2 dogs was 14 hours and 48 minutes and 18 hours and 20 minutes, a period of considerably greater duration than the survival time of the nontreated group (Fig. 5).

The oxygen saturation of the arterial blood of the dog during partial perfusion varied from 40 to 90 per cent and was usually about 50 per cent saturated despite the complete saturation of the blood passed through the extracorporeal circuit. The oxygen saturation of venous blood was 20 to 30 per cent. The arterial blood carbon dioxide content was decreased during the perfusion. The hydrogen ion concentration of the arterial blood did not show an unusually wide variation. The hematocrit remained constant (Fig. 6). The free hemo-

globin remained below 200 milligrams per 100 cubic centimeters of plasma. While being perfused the dog's respiratory efforts ceased. During the terminal portions of the perfusion there was a continuous drop in the systemic systolic blood pressure. The arterial blood oxygen saturation rose during the latter part of the perfusion. This may have been due to a greater proportion of the total systemic circulation passing through the extracorporeal pump and lung.

The postmortem findings in these dogs were similar to those in the nonperfused animals except for the findings in the respiratory system. The trachea and bronchi contained only small amounts of serosanguineous fluid. The parenchyma of the lung was not edematous; however, it was engorged with blood and bled freely when sectioned (Fig. 7).

SUMMARY

A description of satisfactory methods to produce burns of the pulmonary system in the dog is given. The findings following thermal injury to the respiratory tract in the dog are discussed. Survival times of burned dogs receiving no plasma substitute are compared to those receiving a sufficient amount to maintain the hematocrit near the preburn value. Preliminary observations regarding the possible value of a partial extracorporeal circulation as a means of prolonging the survival time are given.

THE COLLATERAL CIRCULATION IN THE ARTERIAL OCCLUSIVE DISEASE OF THE LOWER EXTREMITY

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MODERN treatment of arterial diseases emphasizes the importance of a thorough knowledge of the type and function of the collateral circulation together with its ability to develop as the lesions in the main arteries advance.

The treatment and prognosis will depend upon the anatomic and functional condition of the arterial tree. A direct surgical attempt to re-establish blood flow through the main arteries will be guided by the pattern of the bridging collaterals. The precise knowledge of the location of the functioning and functional collaterals will avoid a waste of time and irreparable errors while surgery is being performed. Injury or severance of a collateral which belongs to a vital detour jeopardizes the function or the life of a limb.

This paper is based on the clinical and concomitant arteriographic study of 50 consecutive patients presenting arterial insufficiency of the legs as the main complaint.

Table I shows the site of occlusion and the incidence. Since the vessels distal to the popliteal artery are of no direct surgical interest because of their size we have grouped them into one unit. In several instances there were multiple lesions on the same side; Table II shows these associations. Thirteen patients (26 per cent) had bilateral lesions.

The collateral branches which are present and functioning in normal humans are well known. It is also known that in a certain number of cases these branches may follow variations as far as origin and distribution are concerned. If the main artery is involved in a pathologic process, these preformed normal collateral branches may hypertrophy and anastomose with one another. At the same time, a network of vessels smaller in caliber and irregular in distribution can develop. Under normal circumstances, these vessels cannot be seen. They belong to the vascular system of the muscles. It has been a matter of discussion as to whether these vessels are newly formed or whether they have always been present but were not functioning. This discussion is academic. It is sufficient for practical purposes to recognize that these vessels functionally are new. For clarity we call the vessels belonging to the first group "*main collateral branches*" and the vessels of the latter group "*accessory collateral branches.*"

If a main artery becomes obstructed, the development of the circulation in its area of supply depends upon five factors: (1) the site of obstruction and length of the block; (2) arteriospasm; (3) etiology of the arterial disease; (4) the therapeutic measures instituted; and (5) the response of the individual.

Site of obstruction and length of the block. It is obvious that, if a thrombosis is established in a large size vessel at the site where a main collateral branch arises and, therefore, blocks its point of origin, the blood supply to the territories distal to it will be jeopardized. At the same time, it is also obvious that the longer the extent of the block the greater are the chances of involving more points of origin of main collateral branches. On the other hand, the length of the block is of little importance if it does not interfere with the "vital detours" of that vascular district.

Arteriospasm. Every lesion of an artery may initiate an arteriospasm. This spasm can be either local or distributed to the

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Fig. 1, left. The main arteries are blocked. The arrows point out areas of hypervascularization formed by a network of accessory collateral branches.

Fig. 2, right. Block of the profunda and of the anterior tibials. The arrows point out the two strategic vessels which originate from the superficial femoral artery and which in this case carry blood to the territory usually supplied by the branches of the profunda. A network of supplementary branches is outlined in the calf.

whole vascular territory distal to the lesion. It can be either temporary or permanent, and it varies in intensity. The spasm affects mainly vessels of small caliber and, therefore, it prevents function and hypertrophy of the main collateral branches as well as development of the accessory collateral branches.

Etiology of the arterial disease. This affects the collateral circulation in two ways: (a) onset and (b) pathologic anatomy. Arterial diseases of sudden onset are much more dangerous than those which occlude slowly. This is due to the fact that a sudden injury to an artery, regardless as to whether it originates from the adventitia (trauma) or intima (embolus or thrombosis), creates a reflex spasm which inhibits the function of the collaterals. On the other hand, a slowly progressing injury of the vessel allows collaterals to develop. Intermittent compression of an artery has been advocated as a way of developing an efficient collateral circulation. As far as the pathologic anatomy is concerned, an arterial disease on an inflammatory basis or associated with inflammatory processes creates more spasmogenic stimuli than a disease which is degenerative in type.

Therapeutic measures. The collateral circulation will improve every time spasm is

TABLE I.—SITES OF OCCLUSION IN 50 PATIENTS WITH ARTERIAL INSUFFICIENCY OF THE LEGS

	No. of cases	Per cent
Common iliac artery	4	8
External iliac artery	7	14
Common femoral artery	4	8
Superficial femoral artery	36	72
Profunda	3	6
Popliteal artery	10	20
Distal to popliteal artery	19	38

TABLE II.—SITES OF MULTIPLE UNILATERAL LESIONS

	No. of cases
Common and external iliac arteries	3
Iliac and femoral arteries	6
Superficial femoral and popliteal	9
Superficial femoral artery and/or popliteal artery and distal vessels	12
Profunda and superficial femoral	1
Profunda and popliteal artery	1
Profunda and distal vessels	1

a b c

d

Fig. 3. a, Block of the popliteal artery. Only supplementary branches carry blood to the periphery; prognosis poor. b, Block of the popliteal artery. The arrow points out the descending branch of the superior articular artery which is hypertrophied; prognosis fair. c, Block of the popliteal artery. Anterior and posterior tibial arteries are patent and receive their blood supply through supplementary branches which in this case function like bridging collateral; prognosis good. d, Segmental obstruction of the external iliac and common femoral. The arrow points out the realignment of the superficial femoral artery.

relieved either by medical or surgical means. Both the main and the accessory collateral branches will benefit by this treatment. Blood flow through the main collateral branches can be improved by direct surgical attack even in those cases in which the obstruction of the main artery cannot be completely removed.

The response of the individual. There are individual variations to the same kind of stimuli and, therefore, there are instances in which there is a very poorly developed collateral circulation, even following treatment and without any plausible reason. The prognosis in these cases is poor. There are patients in whom a very rich collateral circulation may even disguise the presence of an occlusive arterial disease.

The collateral circulation shows mainly three types of distribution, whether or not

the main collateral branches or accessory collateral branches are participating in its formation: (1) areas of hypervascularization, (2) supplementary branches, and (3) bridging collaterals.

Areas of hypervascularization. These areas are mainly formed by accessory collateral branches, very small in size, which carry blood to a territory (bone, muscle, or skin) the normal blood supply of which has been cut off. It is actually very difficult to identify the vessels, but the area can be identified by an arteriogram because of the concentration of dye in a certain territory (Fig. 1). Since at the time of surgery these vessels usually cannot be identified, they are frequently unknowingly sacrificed. Their severance, however, does not severely compromise the function of the part because they frequently are re-established. These areas benefit from any procedure that releases vasospasm.

Supplementary branches. These branches may arise either from main or from accessory collateral branches and they are large enough to be identified on the arteriogram. They vary in size and distribution but usually run parallel to the obliterated main artery.

The arteriogram reproduced in Figure 2 shows a complete obstruction of the femoral profunda, which is the artery that normally supplies blood to the muscular structures of the thigh, and block of the anterior tibial artery. Only one collateral branch, the great anastomotic artery, arises from the superficial femoral artery under normal circumstances. In this case, at the midthigh, two collateral branches take over the function of the profunda while in the leg a network of supplementary branches carries out the blood supply to the calf. These two vessels which originate from the superficial femoral artery are often encountered and further discussion of these will follow when we describe the bridging collaterals. In this case (Fig. 3a) they function as supplementary branches and do not participate in the formation of a vital detour, the superficial femoral and popliteal arteries being patent.

If there is a block of the popliteal artery, several possibilities are open for the collateral circulation to develop. One is represented by the supplementary branches alone, with the main arteries partially or completely occluded (Fig. 3a). This condition is sometimes improved by the hypertrophy of one or more articular arteries. Figure 3b shows the descending branch of the superior articular artery and its distribution to the muscle groups of the calf.

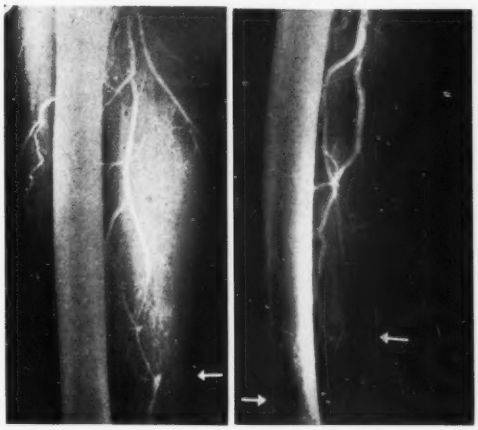

Fig. 4, left. Segmental obstruction of the superficial femoral artery. The arrow points out the functional realignment of the superficial femoral artery distal to the block through the vital detour, profunda to perforating branch to bridging artery to superficial femoral.

Fig. 5, right. Segmental obstruction of the superficial femoral artery. One arrow points out the same vital detour as in Figure 4. The other arrow points out the second vital detour, profunda to descending branch of the lateral femoral circumflex artery to second bridging artery to superficial femoral.

Occasionally, there may be a perfect functional realignment of the anterior and posterior tibial arteries following a complete obstruction of the popliteal artery. In this case (Fig. 3c) supplementary branches are seen to function like bridging collaterals.

Bridging collaterals. Most of these collaterals are formed by main collateral branches. These bridging collaterals delimit a segmental obstruction of a main artery and are actually responsible for the functional diversion of the blood flow at the site of a block and for the functional realignment of the main artery distal to the obstruction. The blood flow is reversed in those bridging collaterals which originate from the main ar-

Fig. 6, left. Short segmental obstruction of the superficial femoral artery between the origins of the strategic bridging arteries (see arrows).
Fig. 7, right. Superficial femoral artery and bridging arteries (arrows) at the time of surgery. Figure 8 shows the arteriogram of this case.

tery distal to the block. A vital detour is established every time a segmental obstruction occurs in a main artery between the points of origin of collateral branches which participate in the formation of the most frequently encountered vital detours.

Figure 3d shows a segmental obstruction of the distal third of the external iliac artery and the proximal third of the common femoral artery. Functional realignment distal to the block is obtained through numerous bridging collaterals (see Table III).

The angiographic findings concur with the anatomic description of the collateral branches with the exception of one vessel which has proved to be of extreme interest and which arises from the superficial femoral artery at the junction of its middle and distal thirds. Occasionally a second vessel with the same function arises about 2 centimeters distal to the first one and follows the same distribution (Fig. 2).

Figures 4 and 5 show such vessels as part of a vital detour. In both cases, there is a complete obstruction of the proximal two-thirds of the superficial femoral artery. In both cases, one of the two vessels is anastomosed to the fourth perforating branch of the profunda, and in Figure 5 there is a double vital detour, the second of these vessels being anastomosed to the descending branch of the lateral femoral circumflex artery.

In 1 instance (Fig. 6) we have seen a segmental block of the superficial femoral artery limited to a very short segment between the origin of the strategic bridging arteries. This finding, as well as the others, was confirmed at the time of surgery, and one can see (Fig. 7) the two vessels exposed with the block of the main artery in between.

A segmental obstruction of the distal third of the superficial femoral artery can be seen in Figure 8 with realignment of the popliteal artery through the bridging ar-

Fig. 8, left. Segmental block of the distal third of the superficial femoral artery. The arrows point out the vital detour which allows realignment of the popliteal artery (superficial femoral artery to bridging collateral to superior genicular to popliteal artery).

Fig. 9, right. Segmental obstruction of the popliteal artery. The arrow points out the great anastomotic artery through which the functional realignment of the vessels distal to the block is obtained. The vital detour is formed by superficial femoral to great anastomotic to inferior genicular to popliteal artery.

teries and the medial superior genicular artery. Figure 9 shows a segmental block of the popliteal artery with complete realignment of all the main arteries distal to the block. This realignment is obtained by a vital detour of the superficial femoral to the great anastomotic to the inferior genicular to the popliteal artery, and provides good vascular function for this lower extremity.

DISCUSSION

The fundamental types of collateral circulation noted in arterial disease have been shown. The prognosis and indications for treatment depend upon the pattern of these types. At present, arteriography is the only means to determine them with accuracy.

As far as treatment is concerned, the first type of collateral circulation (areas of hypervascularization) will benefit only from procedures which release vasospasm, and an attempt at either removal of the obstruction (embolectomy or intimectomy) or bridging of the main artery by graft will not be indicated. The second type (supplementary branches) can be improved not only by releasing the vasospasm but also by direct surgery on the main artery, even if the obstruction cannot be entirely removed. In fact, partial removal of an obstruction may open the origin of a main collateral branch thus increasing the blood flow toward the periphery. Sometimes this may also help to establish a vital detour which was not present because the origin of one of the bridging collaterals was blocked. The third type of collateral circulation (bridging collaterals) delimits a segmental block of the

TABLE III.—TYPES OF COLLATERAL CIRCULATION IN ARTERIAL DISEASE

Site of block	Origin of vital detour	Bridging collaterals		Realigned main artery
		Direct flow	Reversed flow	
Common iliac*	Abdom. aorta	Middle sacral	Lateral sacral	Internal iliac
	Abdom. aorta	Lumbar arteries	Deep iliac circumflex	External iliac
	Inf. mesenteric	Sup. hemorrhoidal	Inf. hemorrhoidal	Internal iliac
	Abdom. aorta	Ovarian artery	Uterine artery	Internal iliac
External iliac*	Common iliac	Iliolumbar artery	Lateral circumflex	Profunda
	Internal iliac	Superior gluteal	Lateral circumflex	Profunda
	Internal iliac	Inferior gluteal	Medial circumflex	Profunda
	Internal iliac	Obturator artery	Medial circumflex	Profunda
	Internal iliac	Internal pudendal	External pudendal	Common femoral
Common femoral	Common iliac	Iliolumbar artery	Lateral circumflex	Profunda
	Internal iliac	Superior gluteal	Lateral circumflex	Profunda
	Internal iliac	Inferior gluteal	Medial circumflex	Profunda
	Internal iliac	Obturator artery	Medial circumflex	Profunda
	External iliac	Deep iliac circumfl.	Lateral circumflex	Profunda
Superficial femoral (proximal and/or middle three)	Profunda	Descending branch of lat. circumfl.	Bridging artery	Superficial femoral (distal third)
	Profunda	4th perforating branch	Bridging artery	Superficial femoral (distal third)
Superficial femoral (distal third)	Superficial fem.	Bridging artery	Med. sup. genicular	Popliteal artery
	Superficial fem.	Great anastomotic	Inf. genicular	Popliteal artery
	Profunda	Descending branch lateral circumfl.	Med. sup. genicular	Popliteal artery
Popliteal artery	Superficial fem.	Great anastomotic	Inf. genicular	Popliteal artery
	Popliteal artery	Superior genicular	Inf. genicular	Popliteal artery

*There are numerous indirect anastomoses between right and left internal iliac arteries through their main branches.
Examples of all types of bridging collaterals listed in this table have been included in the 50 cases herein reported.

main artery. The latter can be successfully removed by direct surgical attack thus re-establishing a good circulation in the leg.

To know the point of origin and the distribution of the main collateral branches and to recognize those branches which potentially may participate to the formation of a vital detour helps to interpret an arteriogram and inspire a rational, specific, and often successful surgical treatment.

SUMMARY

1. The sites of obstruction and their incidence in arterial occlusive disease of the lower extremity have been reported.

2. The factors which determine the function of the collateral circulation have been discussed.

3. The different types of collateral circulation encountered in arterial disease have been demonstrated.

4. The pattern followed by the bridging collaterals in the formation of the vital detours have been documented.

5. The importance of the knowledge of the distribution of the main collateral branches in the interpretation of arteriograms, both before and at the time of direct surgery upon the main arteries, has been emphasized.

EPITHELIAL TUMORS OF THE EYELIDS

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MOST malignant lesions of the skin are superficial, slow growing, and easily diagnosed. They have a high rate of complete curability when diagnosed early and treated properly. Considering these facts, the present formidable mortality and tremendous morbidity from these lesions offer a challenge to the medical profession.

Approximately 85 per cent of all skin cancers are found in the regions of the head and neck. The incidence of epithelioma of the eyelid is estimated by various authorities to be from 2.5 to 16.8 per cent. In reviewing 815 cases of cutaneous epitheliomas at the Presbyterian Hospital in New York City, one of the authors found an incidence of 7 per cent. Epithelioma of the eyelid cannot, therefore, be considered an uncommon clinical entity.

Lesions of the eyelid usually attract the early attention of the patient because of their exposed position on the face and their frequent interference with normal lid function. At this juncture, a complete excision may be performed with minimal lid deformity or functional disturbance. When, however, through a patient's ignorance or reticence or a physician's timidity and inadequate therapy, the lesion extends to invade deep eyelid structures, orbital contents, or orbital bone, a cure may be effected only by more radical procedures and by full thickness reconstructions. The presence of a functioning eyelid is indispensable to good vision; therefore, the surgeon is faced at this point with a difficult and challenging problem.

It is the object of this paper to analyze 60 cases of epithelioma of the eyelids treated by the authors, with special reference to total and subtotal reconstruction.

Incidence. There is no significant difference in the incidence of epithelioma of the eyelid between sexes. Women are subject to the disease with the same frequency as men, although in our series the ratio of male to female is 3 to 2.

The highest incidence of epithelioma of the eyelid in our series occurred in the sixth decade. The distribution by age of these 60 cases was as follows: 3 were from 21 to 30 years of age, 5 from 31 to 40, 10 from 41 to 50, 20 from 51 to 60, 12 from 61 to 70, 7 from 71 to 80, and 3 were over 80 years old. Driver and Cole found their highest incidence in the seventh decade while del Regato found his in the eighth decade.

Regional distribution. The lower eyelid and the inner canthus are the regions most commonly involved in neoplasms of the eyelid. In our series 60 per cent (36 cases, 5 involving deeper structures) of the epitheliomas occurred on the lower lid and 20 per cent (12 cases, 1 involving deeper structures) at the inner canthus. The other 20 per cent involved the outer canthus in 3 cases (5 per cent), the upper eyelid in 4 cases (7 per cent), the eyebrow region in 2 cases (3 per cent), and both eyelids in 3 cases (5 per cent) in which the deeper structures were involved. This distribution of eyelid lesions has been similarly reported by Birge, Stetson and Schultz, Hunt, Driver and Cole, and del Regato. We believe that the wearing of improperly fitted eyeglasses, producing constant pressure and irritation at the inner canthus, may be a significant factor in the etiology of inner canthal lesions. The inner canthus and lower lid are subject to chronic irritation from eye discharges, which may also have etiologic significance. The upper lid and outer canthus, on the other hand, are usually free of such stimulation.

Histopathology. Every lesion in this series of 60 cases was examined microscopically. Basal cell epithelioma was the most frequent lesion encountered; it was noted in 42 lesions (70 per

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a b c

Fig. 1. Full thickness skin graft. H.L., a 52 year old male, admitted to the hospital with an ulcerative basal cell epithelioma of the right lower eyelid, of 3 years' duration, a. The lesion was excised and the defect grafted with full thickness skin from the upper right eyelid. b and c, A 4 year follow-up has revealed no evidence of recurrence, and the cosmetic and functional results are excellent.

cent of the cases). Squamous cell epithelioma was noted in 5 lesions (8.3 per cent), basosquamous cell epithelioma in 1 lesion (1.7 per cent), hyperkeratotic papillomas in 8 lesions (13.4 per cent), neuronevi in 4 lesions (6.6 per cent). La Cassagne pointed out that eyelid skin has an extremely thin epidermis. It was his opinion that outside irritations such as sunlight, pressure, or trauma may easily disturb the basal cell layer through this thin epidermis and subsequently result in a basal cell epithelioma in this region. Morax was of the opinion that a basal cell lesion of the eyelid arises primarily from the meibomian sebaceous glands and more rarely from the glands of Zeis or sweat glands of Mall.

A basal cell epithelioma is a localized neoplasm. It extends primarily by direct infiltration. In the eyelids, it may involve the tarsal plate and conjunctiva. At the canthus, it may become adherent to the underlying bone. Late lesions may show local permeation along the adjacent lymphatics which may explain paramarginal subcutaneous extension and intraorbital involvement when the affected lymphatics penetrate the orbital fascia.

In our series, there were 9 cases of basal cell epithelioma exhibiting deep structural involvement: 5 lesions invaded to involve the full thickness of eyelid; 1 lesion at the inner canthus invaded the underlying bone; and 3 lesions had massive invasion destroying both lids, with accompanying intraorbital extension.

Squamous cell epitheliomas are usually rapidly growing lesions which infiltrate neighboring structures earlier than the basal cell type. Not infrequently they metastasize to the regional lymph nodes at the preauricular and submaxillary regions. Fortunately, the squamous cell epithelioma is relatively uncommon in the eyelid. None of the 5 cases which were observed in our series showed regional metastasis.

TREATMENT

The primary aim of treatment is complete extirpation of the neoplasm which should be accomplished in the shortest possible time with minimal structural deformity and functional impairment of the eyelids.

In the selection of a form of therapy for the early lesion, the physician may be guided by the availability of experienced therapists, since equally admirable results have been reported by qualified surgeons and radiotherapists. The authors, however, favor surgical excision for the following reasons:

1. Complications, such as cataract, extensive and deforming cicatrization of the eyelid, persistent conjunctivitis, and stenosis of tear duct, are still of a sufficiently high incidence to present a problem after a curative dose of irradiation.

2. Since the treatment of these lesions with irradiation is generally performed without the benefit of a biopsy, the physician is deprived of a microscopic confirmation of the clinical diagnosis. Radioresistant lesions may be treated for extensive periods of time with prolonged ineffective irradiation, following which the hope of permanent cure may be lost or may be accomplished only with considerable difficulty.

3. Advanced lesions may not be satisfactorily controlled by radiation if they involve

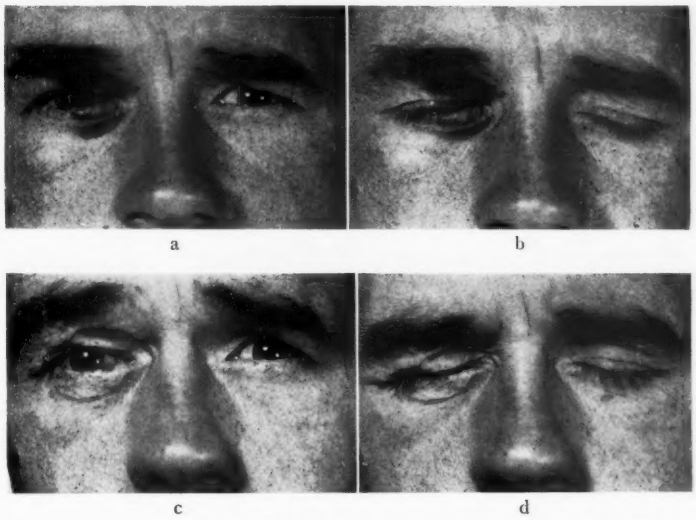


Fig. 2. Full thickness skin grafting and free eyelash grafting. F.T., a 28 year old male, was admitted to the hospital with pigmented nevi of the right upper and lower lids since birth, a and b. A gradual increase in the size of the lesion had resulted in deformity of the lids and narrowing of the palpebral fissure. Eyelashes were absent in the involved areas. Both lesions were excised (at separate stages), and full thickness skin grafts from the postauricular region were used for repair. Three months later, a single layer of hair-bearing free graft was transferred from the left eyebrow to the medial palpebral margin of the right upper lid. All grafts had successful takes. c and d, A 2½ year follow-up revealed an excellent cosmetic and functional result with the remaining normal eyelash indistinguishable from the grafted cilia.

deep structures, such as orbital invasion or facial bone involvement.

4. Following a satisfactory response to radiation therapy by gross examination of the region of the neoplasm, there is no confirmation of complete destruction of the lesion. A sectional examination of the surgical specimen, on the other hand, gives microscopic evidence of the completeness of the surgical excision and provides the soundest basis for accurate prognosis.

5. The present availability of many varied plastic reconstructive procedures makes possible radical extensive excision, which is rarely followed by marked deformity or impaired function, even in advanced cases.

6. When a previously irradiated lesion does recur, it is invariably radioresistant and requires surgery. Surgical excision of such a lesion requires eradication not only of the recurrent lesion, but also of the entire irradiated area, transforming what originally might have been a simple reconstruction to one of major complexity.

FUNCTIONAL ANATOMY

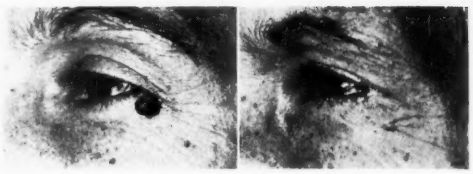
A clear understanding of the structural and functional characteristics of the eyelid is a prerequisite for a successful repair following surgical excision. The eyelids are composed of 2 thin, movable folds of skin and mucous membrane with a firm fibrocartilaginous plate between. There is normally no adipose tissue in the areolar layer. In front of the tarsal plates lies a circular muscle, the orbicularis oculi, for closure of the eyelids. The aponeurosis of the levator palpebris muscle is attached to the upper eyelid and functions to widen the palpebral fissure. At the mucocutaneous junction, there is a single layer of hair which forms lashes. Vision is possible when the eyelids are separated, while protection against injury, foreign bodies, and excess light is accomplished by their closure. The well

a b

Fig. 3.

a b

Fig. 5.



a b

Fig. 4.

Fig. 3. A flap shift for inner canthal lesion. S.T. was a 67 year old housewife with a 1.8 centimeter superficial basal cell epithelioma of the right inner canthus, a. The lesion had been present for a year and had grown slowly. There was no previous treatment. The neoplasm was excised and the defect repaired with a pedicle flap rotated from the upper eyelid. The donor area was closed without tension. b, Two year follow-up revealed no recurrence and an excellent cosmetic and functional result.

Fig. 4. Pedicle flap for outer canthal lesion. M.M., 33 year old female, was admitted to the hospital with a slowly enlarging basal cell epithelioma of the left lower eyelid of 2 years' duration, a. The lesion was excised and the defect repaired with a pedicle flap transferred from the upper lid. The donor area was closed primarily without tension. b, The postoperative course was uneventful, and a 2 year follow-up has revealed no recurrence and a good cosmetic and functional result.

Fig. 5. Multiple pedicle flaps for inner canthus lesion. J.M., 78 year old male, was admitted to the hospital with a basal cell epithelioma of the left inner canthus and upper eyelid extending on to left lateral side of nose, measuring 1.8 by 1.5 centimeters with involvement of the canthal ligament, a. He had received no previous therapy. A wide excision of the tumor was performed, and 5 skin flaps were shifted to repair the defect. Flaps were shifted from the upper and lower eyelids, the forehead, and the lateral aspect of the nose. A cheek flap was also advanced. The patient had a satisfactory cosmetic and functional result. b, A 10 year follow-up reveals no sign of recurrence.

being of the cornea depends upon a constantly moist environment, which is provided by the reflex blinking of the upper lid, repeatedly bathing the cornea in the secretion of the tear ducts. The eyelashes function as a screen against air-borne foreign bodies. Thus a perfectly functional eyelid must be thin, mobile, and lined by smooth conjunctiva. The chief function of the upper eyelid is mobility, and it is responsible for almost 90 per cent of the opening and closing movement. The overlying skin must be without tension and loosely attached to the tarsal plate to allow gliding during motion. The chief function of the lower eyelid is support; this is accomplished by an active orbicularis oculi muscle and a firmer tarsal plate than is present in the upper lid. The skin of the lower eyelid is thicker and less relaxed than that of the upper. In surgery of the eyelids, the following points deserve emphasis:

1. A much wider segment may be excised from upper than from lower lid, and defect closed primarily without danger of ectropion.

2. If a free skin graft is needed to repair a surgical defect in an eyelid, the thicker the graft, the less the resulting contracture, and the more successful the final result. A full thickness graft from the eyelids, the clavicular area, or the postauricular region will furnish an ideal functional and structural graft and will be a good color match.

3. A pedicle skin graft with adipose tissue in the subcutaneous layer is not suitable for eyelid repair since it increases the thickness of the lid, thereby decreasing mobility.

4. In subtotal or total reconstruction of the upper eyelid, a firm attachment of the apo-

a b

Fig. 6. Radical excision with enucleation of the orbit. J.L., a 72 year old male, was admitted to the hospital with a 3 year history of a progressively enlarging and ulcerating lesion of both left eyelids. Twenty-two years before admission, the patient sustained molten metal burns to both lids. a, The patient had a multicentric, rapidly growing basal cell epithelioma of the inner canthus invading both eyelids and the canthal ligament and extending into the orbit. There was no bone involvement demonstrable. The entire lesion including both eyelids, the inferior and superior orbital ridges, the nasolacrimal bone, and the entire orbital contents were excised in toto. The entire denuded area was covered with split thickness skin graft. b, Pathologic report confirmed adequate excision, and a 2 year follow-up has revealed no evidence of recurrence.

a b

Fig. 7. Radical excision with enucleation of the orbit. P.M., a 65 year old male was admitted to the hospital with a basal cell epithelioma of the right lower eyelid, of 12 years' duration. The patient had previous therapy of an undetermined nature. Examination on admission revealed that the lesion extended from a completely destroyed right lower lid around the lid margins to involve both canthi and portions of the upper eyelid. a, The right side of the nose was invaded and the lesion was fixed to the right nasal and infraorbital bones. Extension along the floor of the orbit was palpable. Vision was not impaired. A radical excision including both eyelids and the skin of the right side of the nose and malar prominence, the entire orbital contents and the right infraorbital and nasal bones was performed. The defect was repaired with a split thickness graft. The margins of the excision were pathologically adequate. b, The postoperative photograph was taken 3 weeks after surgery. The patient expired 1 year later following a coronary occlusion.

neurosis of the levator palpebris superioris muscle to the tarsal plate is essential.

5. In reconstruction of the lower eyelid, a good segment of tarsal plate is necessary to provide adequate support.

6. It is more important to preserve the lashes of the upper lid than those of the lower because of the former's function in protecting the eye from foreign bodies.

7. The conjunctiva which lines the eyelids cannot be replaced by a skin graft, since the desquamation and relatively rough texture of the graft serve to irritate the cornea. When eyelid lining is required, a mucous membrane free graft from the oral cavity may be utilized.

TYPES OF SURGICAL PROCEDURES

In the present series of 60 cases, surgical excision of the lesion, was exclusively employed.

Excision and closure. Simple excision followed by primary closure was performed in 22 cases. These were all small, early, well local-

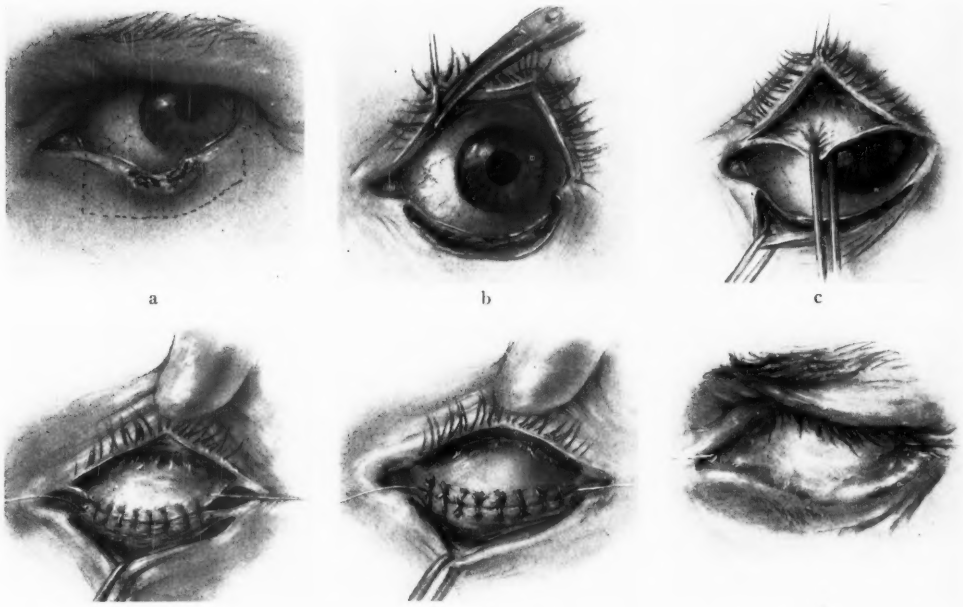


Fig. 8. Subtotal reconstruction of the lower eyelid—stage I. a, A neoplasm involving full thickness of lower eyelid and proposed lines of excision. b, The lesion excised causing a defect in the lower lid. Extension of incision along intermarginal white line of upper eyelid. c, Mobilized tarsoconjunctival flap drawn downwards to approximate conjunctiva of lower lid defect. d, Approximation of tarsoconjunctiva of upper lid with conjunctiva of lower lid defect using fine stainless steel continuous pullout suture. e, Re-enforcing layer of areolar tissue over stainless steel wire suture line (sutured with fine catgut). f, Full thickness graft covering exposed tarsoconjunctival segment and healed.

ized lesions that had not infiltrated the deeper lid structures. A transverse elliptical incision, including the lesion with a safe margin of normal surrounding tissue, was used for lesions of the eyelid proper. An oblique incision was utilized for lesions of the canthi. A relatively large lesion on the upper eyelid may be excised and the incision primarily closed without fear of ectropion. Much less freedom can be employed on lesions of the lower eyelids. Any lesion approaching or including the lid margin is difficult to close primarily without resulting ectropion or distortion of the lid margin.

Excision and full thickness skin grafting. Twenty-three lesions, nearly all large but superficial and noninvasive, were treated by this method. The defects resulting from excising such a lesion cannot be closed primarily. A full thickness graft taken from the eyelid, postauricular, or clavicular region, is trimmed to fit and sutured in place. A pressure dressing is maintained. The first dressing is usually done on the fifth or sixth postoperative day (Figs. 1 and 2).

Excision and flap shift. In certain cases, a pedicle or banner flap can be raised from the upper eyelid and transferred to repair a defect of the lower eyelid. This is especially suitable when the recipient site is not ideal for a full thickness free skin graft. This situation would be present in areas which have been heavily irradiated or where bone is exposed as a result of wide surgical excision. A local pedicle flap was employed to repair the defect in 7 cases of this series (Figs. 3, 4, and 5).

Radical excision with enucleation of the orbit. This procedure was used in 3 instances. Advanced lesions with involvement of orbital content and neighboring bony structures are definitely curable if the lesion can be completely excised en block. For the basal cell epithelioma, a prophylactic radical neck dis-

a b c

Fig. 9. Subtotal reconstruction of the lower eyelid—stage II. a, Elevated pedicle flap from upper lid, with a single row of hair at its superior margin, in the process of transfer to its position on the newly constructed lower lid. b, Primary closure of donor area and suture of transferred banner flap in position on newly constructed lower lid. c, Replacement of nonhair-bearing portion of pedicle flap to its original position on upper eyelid.

a b c

Fig. 10. Subtotal reconstruction of the lower eyelid—stage III. a, Incision through healed full thickness graft down to tarsal plate is made between normal upper lid lashes and reconstructed lower lid lashes. b, Division of tarsal plate is accomplished with a small blunt scissors to avoid injury to the globe. c, After division of graft and tarsoconjunctiva the lids are everted to show segment of cartilage and conjunctiva transferred to lower eyelid.

section is not necessary. Plastic reconstruction of the resulting deformity is usually not indicated in patients of advanced age. The primary application of a split thickness graft, however, may greatly shorten the convalescent period and increase the physical and mental comfort of the patient (Figs. 6 and 7).

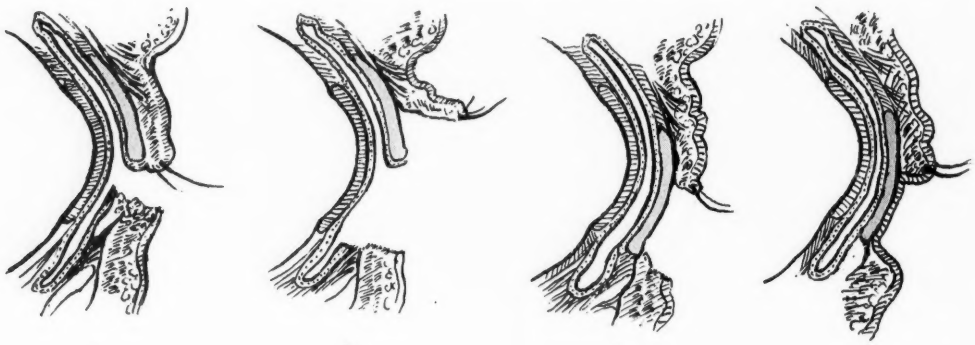
Excision and subtotal and total eyelid reconstruction. This procedure was used in 5 cases of this series. Though eyelid reconstruction has been a problem for centuries, it was not until the turn of the nineteenth century that useful contributions to the technique of blepharoplasty began to appear. These early efforts consisted primarily of local flap shifts and pedicle coverage. The three methods chiefly employed were:

1. Local flap shifts were first described by Carl von Graefe in 1818, when he reconstructed a lower lid with a cheek flap. His method was elaborated upon by J. C. G. Fricke who introduced a procedure for both upper and lower lid reconstruction, using zygomatic and temporal flaps.

2. The sliding flap, one of the earliest of plastic surgical procedures, was utilized at this period for lid reconstruction.

3. The Italian method (using a pedicle from the arm to reconstruct the lid) was a noteworthy contribution of the early nineteenth century and was used extensively by the surgeons of the period.

With these early successes in eyelid reconstruction came an awareness of the necessity



a b c d

Fig. 11. Subtotal reconstruction of lower eyelid. A sagittal section of the eyelids showing the described method of full thickness reconstruction. a, Ulcerated epithelioma involving full thickness of lower lid. b, Full thickness defect at the lower eyelid after radical excision of the malignant lesion. Reflection of skin of upper lid and mobilization of tarsoconjunctival plate. c, Advancement of tarsoconjunctival segment and suture to the conjunctival edge of the lower lid defect. d, Full thickness skin graft to exposed tarsoconjunctival segment.

of muceous membrane coverage of the inner surface of the new lids. Free grafting had not yet been introduced, and various procedures of undermining and rearranging the conjunctiva were attempted in an effort to obtain an adequate lining.

The use of large pedicle flaps, though generally successful, had several disadvantages: (1) The reconstructive procedures frequently caused considerable discomfort for the patient (especially the Italian method); (2) The skin transplanted was frequently a poor match with the normal lid skin in color, texture, and thickness; (3) Scars, some extremely deforming in themselves were produced at the donor sites; (4) Lid function was frequently poor because the reconstructed lid was thick and nonpliable.

Following Reverdin's report of 1869, introducing the concept of free grafts, many attempts were made by the surgeons of the period to utilize that principle in eyelid reconstruction. George Lawson is credited with the first successful use of a free split graft in a case of ectropion in 1870. There followed other successes but many surgeons found the method fraught with difficulties and it was not until the principles of grafting full thickness skin were understood and employed that the percentage of good results with free skin grafts exceeded those obtained with pedicle flaps.

The early period of free skin grafting witnessed the use of donor areas from various locations, the arm and leg being particularly popular. The poor cosmetic and functional results produced by this type of skin led Gradenigo in 1870 to utilize eyelid skin for grafting an eyelid defect. He was the first to introduce the modern principle of eyelid reconstruction: no tissue can replace eyelid tissue as well as normal eyelid tissues. Eyelid skin was used by him as well as other surgeons with good success in the form of both pedicle flaps and free grafts. This concept was further expanded and developed when in 1901 Cirincione split an upper lid and used portions of the tarsoconjunctiva for the reconstruction of an inner layer of lower lid. In 1904, Ischreyt reversed the procedure and reconstructed an upper lid defect in a similar manner. This marked the beginning of whole thickness eyelid reconstruction. In the years that followed, the utilization of the principles mentioned added immeasurably to the success of blepharoplasty.

The contributions of such surgeons as Dupuy Dutemps, John M. Wheeler, and most recently and significantly, Wendell L. Hughes, to mention only a few, have served to refine the techniques of plastic surgery of the eyelids to the high point of effectiveness that they have now reached.

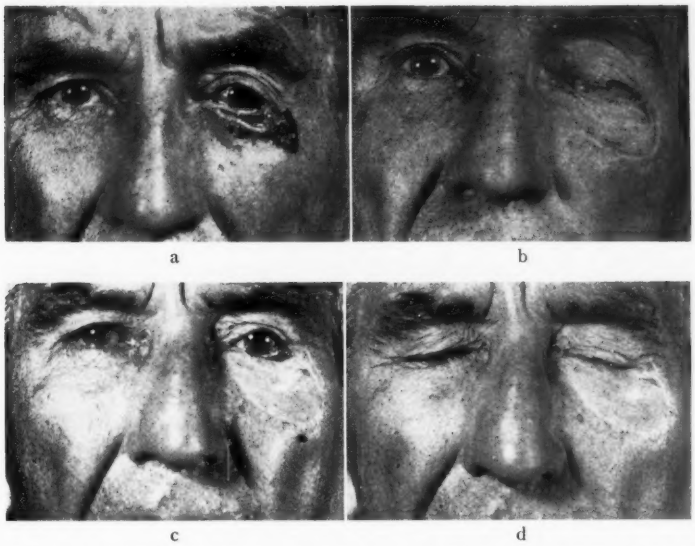


Fig. 12. Subtotal reconstruction of lower eyelid. a and b, J.C., a 70 year old male, was admitted to the hospital with an ulcerative basal cell epithelioma involving the outer two-thirds of the left lower eyelid. Lesion had been present for 4 years and a course in radium therapy had been administered. The full thickness of eyelid was involved by the neoplasm. The lesion was excised and the full thickness defect was reconstructed in two stages by the authors' method. c and d, An 18 month follow-up revealed no recurrence, and the cosmetic and functional results are excellent.

AUTHORS' TECHNIQUE OF EXCISION AND TOTAL AND SUBTOTAL RECONSTRUCTION

The operation to be described in three stages as well as the accompanying illustrations deals with full thickness defects, total or subtotal, of the lower eyelid.

Stage I. The neoplasm is excised in toto with a safe margin of normal tissue producing a full thickness defect of the lower lid (Figs. 8a, b, and 11a, b).

The upper lid is incised at its edge along the intermarginal white line in order to form a tarsoconjunctival and a skin subcutaneous layer. The mobilization of the skin and orbicularis oculi muscle from the tarsus should be sufficiently extensive to allow adequate tarsus for the lower lid repair. Care must be exercised to avoid damage to the levator muscle during this dissection (Figs. 8b, c, and 11b).

The incised edge of the tarsoconjunctival segment of the upper lid is then sewn to the remaining conjunctiva of the lower lid using a No. 36 stainless steel wire continuous running suture, which can be pulled at either canthus. It may be necessary to mobilize the conjunctiva from the globe to accomplish this step (Figs. 8d and 11c). A layer of areolar tissue attached to the tarsal plate is approximated with interrupted No. 5-0 plain catgut as a second layer to reinforce and insure the first suture line (Fig. 8e). A 2 to 3 millimeter opening is left in the conjunctiva at either the nasal or the temporal side for drainage, depending upon the location of the eyelid defect being repaired.

The eyelash margin of the skin of the upper lid is then sewn to the tarsus of the upper lid at such a level that not more than the inferior one-half of the tarsal plate is exposed. Interrupted sutures of No. 5-0 plain catgut are used.

A full thickness skin graft is then taken from the posterior auricular or clavicular area (if the defect is small, the upper eyelid may be used as the donor area) and is sutured in place over the exposed tarsus with No. 6-0 contin-

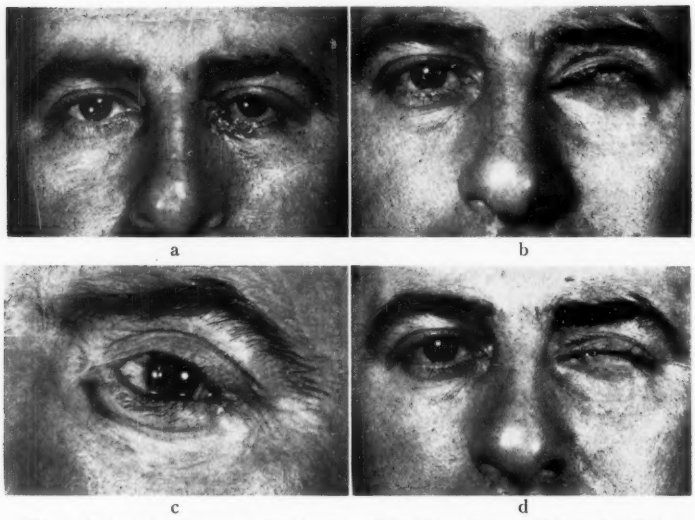


Fig. 13. Subtotal reconstruction of lower eyelid with eyebrow pedicle graft. P.A., a 40 year old male, had been operated upon for a cancer of the left lower eyelid 2 years previously. a and b, On admission, he presented the picture of an unrepaired defect of the left lower lid within which was recurrent basal cell epithelioma. The entire area was re-excised, producing a full thickness defect of two-thirds of the lower lid. This was reconstructed by the authors' method. In addition a pedicle flap, delayed twice, was transferred from the upper lid carrying 1 row of eyebrow hair for reconstruction of the lower lid lashes. c and d, A 4 year follow-up has revealed no recurrence and an excellent cosmetic and functional result.

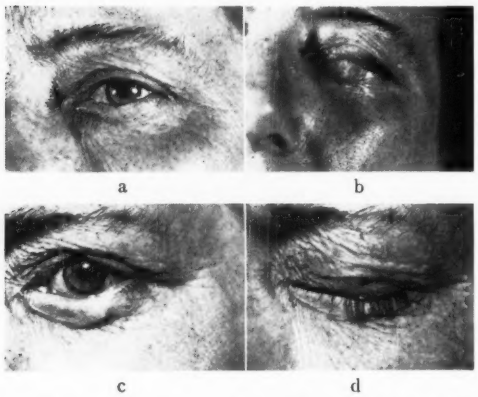


Fig. 14. Subtotal reconstruction of lower eyelid. A.S., 55 year old female, with recurrent basal cell epithelioma of left lower lid, treated 11 years earlier with radiation. Recurrent lesion had been unsuccessfully treated with irradiation 6 months before admission, and 2 months later by inadequate excision. a and b, Patient admitted with palpable and visible recurrent neoplasm of left lower lid involving punctum. Excision and subtotal reconstruction was done in 2 stages. c and d, No further recurrence and good functional and cosmetic result at 2 year follow-up.

uous locked silk sutures. Pressure is maintained by interrupted tie-over silk sutures over a stent dressing. The lashes of the upper lid are carefully everted to prevent incorporation in the graft or the dressing (Figs. 8b and 11d).

A pressure dressing is applied to the entire eye region. In from 7 to 14 days the stainless steel "pull out" wire is removed.

Stage II. Eyelash reconstruction may be attempted in young individuals or in those for whom appearance is an important consideration. This is better done by means of a pedicle flap from the eyebrow rather than a free transplant. A flap is outlined on the upper lid incorporating a single row of hair follicles from the eyebrow along its upper margin. This requires one or two delays before its transfer. A primary delay may be performed during stage I of the procedure. The flap is transferred to the area between the upper lid eyelash and the edge of the full thickness graft, the superior border of the flap carrying

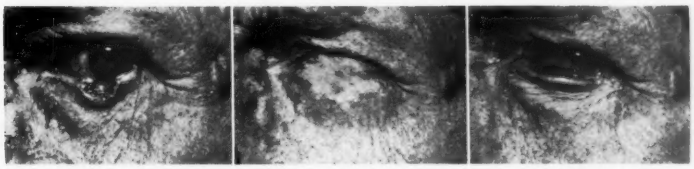


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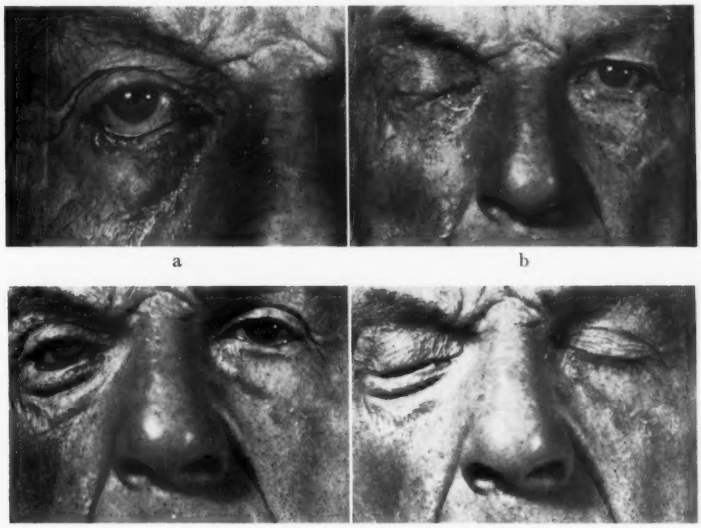
Fig. 15. Subtotal reconstruction of the lower eyelid. E.A., a 75 year old male, was admitted to the hospital with an ulcerative basal cell epithelioma of the left lower eyelid involving the full thickness and more than one-half of the width of the lid, a. There had been no previous therapy. The lesion was of 5 months' duration. Similar basal cell epitheliomas were present on the regions of the nose and left temple. b, The eyelid lesion was excised and reconstructed in two stages. c, A 5 month follow-up revealed no recurrence, and the functional and cosmetic results have been excellent.



a b

c d

Fig. 16. Subtotal reconstruction of lower eyelid. J. D., a 67 year old male was admitted to the hospital with an ulcerative basal cell epithelioma of the right lower eyelid involving the punctum and inner canthus and one-third of the lower lid skin, a and b. The lesion was of 3 months' duration. A radical excision and two stage reconstruction was performed. The patient subsequently developed a mild ectropion of the lower lid which necessitated another full thickness skin graft. c and d, A 2 year follow-up has revealed no recurrence and a satisfactory functional and cosmetic result.

eyebrow cilia to form the lower lid lashes (Fig. 9a). The defect in the upper lid is closed with No. 6-0 silk and the flap is sewn in place with the same size suture (Fig. 9b). In approximately 1 month, the portion of the pedicle flap which does not carry the cilia may be returned to the upper lid (Fig. 9c).

Stage III. Six weeks after stage I, or 4 weeks after stage II, an incision is made through the full thickness of reconstructed lid immediately below the lashes of the upper lid. No suture is necessary for the exposed lid margins thus produced (Fig. 10a, b, and c).

One notes from the technique just described that certain modifications of the original Hughes procedure for eyelid reconstruction have been employed by the authors.

1. An immediate full thickness skin graft for the repair of the defect over the exposed tarsal plate is used. An adequate excision of a malig-

nant lesion, if it has invaded the full thickness of the lower eyelid, generally results in a defect that cannot be effectually covered by the advancement of a cheek flap as originally advocated by Hughes. Tension is usually too great and ectropion of the reconstructed lower lid is almost unavoidable.

The subcutaneous layer of the infra-orbital skin is considerably thicker than normal eyelid skin and will generally produce a poor cosmetic and functional result.

The use of an immediate graft in contrast with a secondary free graft, as advocated by Dupuy Dutemps, shortens the total duration of the lid reconstruction considerably. A well approximated tarsoconjunctiva suture line insures the successful take of the full thickness graft. In all 5 of our cases (Figs. 12 to 16) grafting was carried out without loss.

2. Eyelash transplants are not routinely performed in all blepharoplasties, since eyelashes are not essential to the function of the lower lid. Whenever a transplant is indicated, as in younger patients for cosmetic reasons, a hair-bearing flap shift from the upper eyelid is the chosen method. Free grafts of hair-bearing skin often result in the loss of a portion of the hair follicles. In the case of eyelash transplant involving a single row of hair, such a loss would be equivalent to a complete failure.

3. The use of a continuous, running, removable stainless steel wire for the conjunctiva approximation completely avoids the bulbar conjunctival irritation which so frequently follows the use of interrupted silk sutures. The wire sutures cause minimal tissue reaction, as evidenced by the uniform take of the full thickness skin graft overlying it and fistula formation is eliminated. The ease with which the wire may be completely removed after wound healing serves as an additional advantage (Figs. 12 through 16).

SUMMARY

1. Sixty cases of epithelioma of the eyelids are presented with a description of the various types of surgical repair that may be used following excision of these lesions.

2. A detailed description of the authors' technique in total and subtotal full thickness reconstruction of the eyelid is presented, stressing the use of the following: (a) immediate full thickness skin grafts for skin coverage, (b) fine stainless steel wire "pull out" suture for tarsoconjunctival approximation, (c) flap shift from the upper lid for eyelash transplant to the reconstructed lower lid.

3. Cases are presented to illustrate the major types of eyelid reconstruction used by the authors.

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CONTROLLED HYPOTENSION BY THE BLEEDING METHOD IN OPERATIONS FOR INTRACRANIAL MENINGIOMAS

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DURING the course of an operation which is accompanied by progressive blood loss, the tendency to bleeding gradually lessens. This is phylogenetic safeguard, since, in nature, leeding constitutes the chief threat to life. his diminishing rate of blood loss is due to ie following sequence of events. As an initial esponse to bleeding there is shrinkage of the ascular bed resulting from generalized neuroenic vasoconstriction. As bleeding continues ie capacity of this neurogenic vasoconstricion is exceeded and blood pressure falls.)uring this course of events a vasoconstrictor ubstance, possibly noradrenaline, appears in ie circulating blood. This humoral factor akes over as the neurogenic mechanism begins o fail. Added to these general effects, the oagulating blood at the site of the bleeding ends to plug the torn vessel. Furthermore, here is released by the clot a powerful, locally acting vasoconstrictor substance "serotonin" which causes the torn vessel to constrict more intensely. Nature has wisely provided that the coronary and cerebral circulations are the last to feel these effects of her efforts to compensate for blood loss (Fig. 1).

Considered in the light of the preceding facts, it would appear that the most physiologic method of reducing unavoidable blood loss during operation should be to call into action these phylogenetic responses of the organism. This can be done by removing some of the subject's blood, by a method which will permit its rapid replacement when needed.

In the experimental animal a method of removing, storing, and then replacing arterial blood was developed by Kohlsteadt and Page. In their study they placed a cannula in the femoral artery of an anesthetized dog, directing it toward the heart, and the animal was allowed to bleed rapidly into a closed reservoir. By this method they rapidly reduced the blood pressure to 50 millimeters of mercury at which it was held for 90 minutes and then still further reduced it to 30 millimeters of mercury for an additional 45 minutes. They found that they could hold the blood pressure at any hypotensive level by maintaining the desired level of pressure in the blood reservoir and allowing the pressure in the arterial tree to come into equilibrium with it. Clotting of the removed blood was prevented by the addition of heparin.

At the end of the procedure, with the animal at the borderline of irreversible shock, the blood was reinfused by raising the pressure in the blood reservoir. This forced the blood back up the femoral artery into the aorta. By this method, the reinfusion of 50 per cent of the removed blood resulted in the recovery of 75 per cent of the animals; whereas when the same amount of blood was reinfused intravenously there was recovery in only 30 per cent. Thus these authors put into practice the notion (suggestion offered by Colonel Sam S. Seeley, U.S.M.C.) that intra-arterial administration of fluids might be preferable to the intravenous method in the treatment of severe shock. The absolute control of arterial pressure afforded the investigator by this procedure suggested to one of us that it could be used to advantage as a safety measure during operations in which the surgeon anticipates serious blood loss.

The application of this method to a human subject undergoing operation was first described in 1946 (1). The method of Page was modified by Hale, for the purpose of reducing blood loss in patients undergoing operation for intracranial meningiomas (Fig. 2). Fur-

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Fig. 1. This dog, under anesthesia, was bled by a cannula in the brachial artery until the intra-arterial pressure was 20 millimeters of mercury. At this time, 10 cubic centimeters of 35 per cent diodrast was injected into the cannula. The excellent filling of the cerebral and coronary vessels is illustrative of their relative sparing by the vasoconstrictive process.

ther experience with this method has proved its efficacy.

Between April 1946 and February 1953, this method, which has been called the "Page procedure," has been employed at the Cleveland Clinic in 161 operations. One hundred and six of these were craniotomies, of which 46 were for intracranial meningiomas. In this series of 161 cases there was 1 death which was attributable to the procedure. In this instance while the blood was being returned by the arterial cannula, the patient died without warning and necropsy disclosed air bubbles in the coronary arteries. A repetition of this experience is prevented by the use of a MacIntosh drip. This contains a glass float which sinks as the last of the blood leaves the reservoir, thus acting as a stopper to prevent the passage of air.

Since the meningioma represents a benign and therefore presumably curable lesion, we believe that the results with this lesion offer the best index as to the value of the Page procedure. In these 46 cases of meningioma there were 4 postoperative deaths. The first death occurred on the third day following the removal of an olfactory groove meningioma; necropsy disclosed an unsuspected postoperative hematoma. The second patient had a postoperative hematoma evacuated 6 hours after the removal of a parasagittal meningioma, but he died from the effects of this complication 24 hours later. The third patient had an olfactory groove meningioma in which a vessel, presumably the opposite posterior communicating artery, was torn as the last nubbin of the tumor was removed from its attachment above the sella turcica. The bleeding point proved to be inaccessible. After a prolonged struggle including 12 blood transfusions, the surgeon finally packed the wound with absorbable gauze and concluded the operation. The patient died within a few hours. The fourth death occurred in a man of 67 years with a recurrent meningioma of the left sphenoid ridge. He exhibited postoperative hemiplegia and aphasia and died 2 weeks following operation of thrombosis of the middle cerebral artery.

Thus, there were 4 postoperative deaths in these 46 cases of intracranial meningioma in which the Page procedure was employed, a mortality of 8.7 per cent and 3 cases of postoperative hemorrhage, an incidence of 6.5 per cent. The average postoperative hospital stay in the recovered cases was 13.4 days.

In the same 6 year period 44 patients with intracranial meningiomas were operated upon without employing the Page procedure. These patients, as a rule, represented less difficult surgical problems in which the procedure was not deemed necessary. There were 6 deaths (13.6 per cent), and 3 postoperative hematomas (6.8 per cent). The average postoperative hospital stay of the patients who recovered was 16.3 days. The causes of death were as follows:

The first patient died of uncontrollable bleeding during the removal of a meningioma of the falx. The second had a very stormy course following the removal of a parasagittal meningioma. He developed quadriplegia, cystitis, thrombophlebitis, and eventually died of

pulmonary embolism 39 days after operation. The third, who developed intracranial hypotension after removal of a parasaggital meningioma, died of coronary thrombosis 19 days after operation. The fourth died of hypothalamic injury on the sixth day following the removal of a suprasellar meningioma. The fifth died on the third day following removal of a meningioma attached to the superior surface of the tentorium. Death was due to cerebral edema and incisural hernia. The sixth died of postoperative hematoma and thrombosis of the sagittal sinus on the third day following removal of a parasagittal meningioma.

Comparison of these two groups shows that with the Page procedure the mortality rate was 8.7 per cent and in a parallel series, representing less difficult problems in which the Page procedure was not considered necessary, the mortality rate was 13.6 per cent. The incidence of postoperative hemorrhage was the same. Of those in whom the procedure was employed, 15 did not require donor blood during or following the operation. Of those in whom the procedure was not employed, only 3 did not require it. The average postoperative hospital stay of the patients who recovered was 13.4 days in those with the Page procedure and 16.3 days in those without.

In the 2 years preceding the first employment of the Page procedure a survey of the records discloses that 24 patients with supratentorial meningiomas were operated upon with 5 deaths, a mortality rate of 20.8 per cent. There were 2 instances of postoperative hematoma.[1]

It can be said that this series is not large enough to be significant. However, the 4 neurologic surgeons on the staff at the Cleveland Clinic who have employed this procedure have found that it makes hemostasis easier, that it shortens operative time, lessens operative trauma, decreases the need for blood transfusions, and diminishes postoperative complications. The intra-arterial cannula affords the anesthetist control of the blood pressure and lessens the need for pressor drugs or donor blood. In addition, the anesthetist has a continuous accurate reading of the patient's intra-arterial pressure. He is not dependent upon the cuff method which is inaccurate when the blood pressure is low.

This procedure is of more advantage in patients with intracranial meningioma than glioma, because the former derives a great portion of its blood supply from extracranial vessels, the circulation of which is more affected by the loss of blood than is the cerebral circulation. We have preferred to employ hypotension induced by one of the ganglion blocking agents rather than the Page procedure in the intracranial approach to aneurysms on the circle of Willis. In these lesions the circulation of the brain, if not already im-

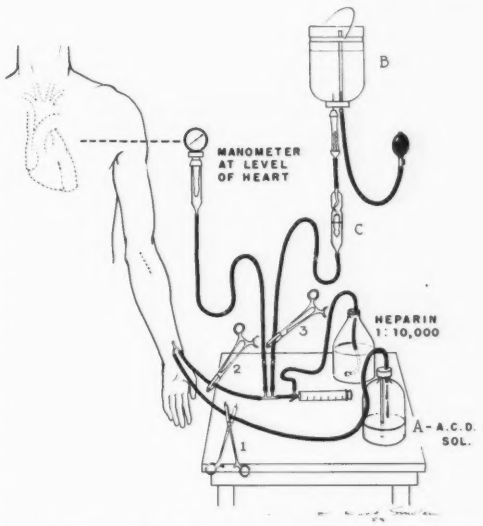

Fig. 2. One arm of the arterial cannula leads to the donor flask *A*. The other arm leads to the manometer, the recipient flask *B*, a container of heparin and a syringe for flushing the system with this anticoagulant. During actual bleeding, clamps *2* and *3* are closed. To observe the intra-arterial pressure, clamps *1* and *3* are closed and *2* is opened. When the first donor flask is filled it is connected to the recipient tubing and bleeding is continued into a second donor flask. The rate of reinfusion of the arterial blood is determined by the difference in pressure in the recipient flask and the radial artery. The MacIntosh drip, *C*, prevents the passage of air.

[1] In the period covered by this survey, 16 patients were operated upon for meningiomas of the posterior cranial fossa. In this series there were 4 deaths, representing a mortality rate of 25 per cent. The Page procedure was not employed in any of these cases because these patients were all operated upon in the sitting position. In this position the bleeding technique is unwise because of the danger of cerebral ischemia. These cases were, therefore, excluded from this survey.

paired by the disease, may be impaired by ligation of the bleeding vessel. Also, to avoid rupture of the aneurysm during its dissection a mean arterial pressure of as low as 40 millimeters of mercury sometimes seems advisable. We have hesitated to lower the blood pressure to this degree by bleeding. But regardless of which hypotensive method is used during operation, we believe that as a safety measure an intra-arterial cannula should always be introduced. This will permit the continuous accurate recording of intra-arterial pressure and will also permit use of intra-arterial transfusion if required. The incision in the radial artery may be closed by suture although no difficulty has resulted from ligating the vessel.

Superficially, it would appear that the vasodilator methods should be safer than the bleeding technique. Surgeons, with their natural repugnance to blood loss, have been slow to adopt a procedure which entails deliberate removal of blood from the circulation. Illustrative of this reluctance, one advocate of the "total spinal method" had referred shudderingly to the Page procedure as the "oligemic shock method."

We would like to stress that during this procedure the patients are not in shock, indeed, far from it. With the blood pressure reduced to 70 or 80 millimeters of mercury and under pentothal anesthesia, there is relatively little pulse acceleration and the patient's skin is pink, warm, and dry. The average amount of blood removed is 1,500 cubic centimeters, the average fall in blood pressure is 33 per cent below the preoperative level.

Our experience leads us to suggest that the Page procedure is the most physiologic, the most certain, and the most readily controllable method of inducing hypotension during operation. It, however, is not the most simple. Interest, aroused by our first publication (1), turned rather toward spinal anesthesia and then to the use of hypotensive drugs as a method of accomplishing the same result.

The use of any hypotensive method is a calculated risk requiring judgment and experience. In experienced hands and in properly selected patients their use improves chances of survival.

SUMMARY

In 46 operations for intracranial meningiomas, the arterial bleeding and reinfusion method was employed to reduce blood loss. There were 4 deaths. The average postoperative hospital stay was 13.4 days. Fifteen patients in this group did not require the use of donor blood. In a parallel series of 44 operations in which the procedure was not employed, there were 6 deaths. The latter series consisted of patients in whom the problem of hemostasis appeared less serious and the procedure, therefore, was not deemed necessary. The average postoperative hospital stay was 16.3 days. Three patients in this group did not require the use of donor blood.

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A CLINICAL REPORT ON THE CYTOLOGIC DIAGNOSIS OF GASTRIC CANCER

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DESPITE the fact that standard roentgenologic procedures provide reliable evidence of gastric cancer in about 9 out of 10 cases, a high mortality rate is still characteristic of this malignant disease. This is due primarily to its relatively symptom-free early course, and to the fact that metastatic spread of the disease may have already occurred by the time recognizable symptoms develop. As a result, perfected techniques for gastric roentgenology have had less effect upon cancer mortality rates than might have been expected.

Our own experience provides a convenient illustration (1). Of 540 cases of gastric cancer seen at the University of California Hospital between 1930 and 1947, only 186 were resectable at the time of diagnosis. Of this group of patients, 134 died in less than 5 years, in the great majority of instances because of recurrence. Five year cures were confined to those patients with a malignant growth at the pyloric end of the stomach. In this location, the growth soon produced marked symptoms of obstruction, and early diagnosis was the result. In other locations, gastric cancer manifests few symptoms until quite late in its course.

For some years it has been felt that cytology might provide an accurate and inexpensive diagnostic method that could readily be applied in private practice. Neither simple aspiration of the contents of the fasting stomach nor saline lavage, however, provided sufficient cellular materials for definitive evaluation. Since examination of surgical and autopsy specimens revealed that the "mucous barrier" covering the gastric mucosa was rich in cellular material (Fig. 1), the problem became one of penetrating this barrier.

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Seybolt, Papanicolaou, and Cooper increased the accuracy of their diagnosis from 32.8 per cent to 60 per cent by substituting intensive lavage with Ringer's solution for simple saline lavage. A comparable efficiency was obtained with an inflatable abrasive balloon, which was passed into the patient's stomach and then rapidly inflated and deflated, thereby mechanically irritating the mucosal surfaces (4).

The chemical nature of the problem involved has led to an extensive search for a stimulant which would induce desquamation of the cellular material in the mucous barrier without distorting cell structure. Hollander, Hess, and Sober have announced that an emulsion of 2 per cent eugenol in water greatly increased the amount of cellular material available over that obtained with a simple saline solution. At the University of California laboratory, excellent results have been obtained with papain.

METHOD

The technique of papain lavage is comparatively simple. A complete discussion of this procedure was presented by Traut and his associates. A paste is made from 3 level teaspoonfuls of papain ground up in a mortar with a little buffer solution. (An electric mixer can be used to advantage.) To this is added 500 cubic centimeters of buffer solution, and the mixture is then filtered after having been stirred or shaken briefly in a closed container. If a heaping teaspoonful of activated charcoal is added before filtering, it will absorb the finer particles of solid and a coarser filter paper can be used. The buffer solution is composed of 750 grams of $Na_2HPO_4 \cdot 12H_2O$ and 0.4 mol (e.g., 400 c.c. of 1 N) of HCL, added to 5 gallons of distilled water. It is believed that this buffer solution protects the cells released from the mucus

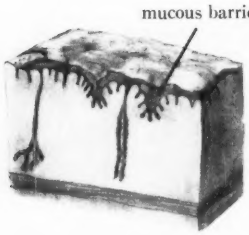

Fig. 1. Gastric cytology. Cells are found in abundance in the thick mucous barrier which lines the mucosa. Mucolytic enzymes, by dissolving this mucous barrier, allow the collection of great numbers of cells for study.

from the action of free hydrochloric acid. This solution may stand for as long as 4 days if it is under refrigeration. Immediately before it is used, 1 gram of cysteine hydrochloric acid should be added to activate the papain.

This filtrate can be instilled into the stomach with a 3 ounce asepto syringe through a Levin tube, after the contents of the fasting stomach have been evacuated. It should be left in the stomach for 10 minutes, with frequent changes of position to insure maximum contact with gastric surfaces. Ordinarily about 450 cubic centimeters of solution can be withdrawn without difficulty. Since papain may cause severe damage to the recovered cells within half an hour, centrifuging should be accomplished as soon as possible.

If the recovered solution cannot be centrifuged in its entirety, a well mixed aliquot will usually yield sufficient cellular material to permit diagnosis. The adhesiveness of the cells can be restored by placing 1 or 2 milliliters of ordinary serum at the bottom of the centrifuge tube. Centrifuging is best performed at about 500 revolutions per minute for 5 minutes by which time, owing to the digestion of the mucus, a layer of cellular material will have formed at the bottom of the tube and a white precipitate at the top. The latter can be washed off with tap water. Slides are prepared and fixed in the usual manner.

Further handling of the slides must be done by specially trained personnel in a fully equipped laboratory. The procedure followed is the same as for any cytologic diagnosis. The usual Papanicolaou technique of staining is used, and preliminary screening can be done by experienced laboratory workers. Suspicious material is marked for final diagnosis by an experienced pathologist.

We have encountered no untoward effects as a result of papain lavage. In several instances blood-tinged returns have been noted, but the bleeding was in every case minor in extent and of short duration. It must be noted, however, that there is a theoretic hazard to the procedure. Since papain is a general protein digestant, there is the possibility that it might dissolve a recently formed thrombus in an eroded vessel. In 2 instances, papain lavage was inadvertently performed on patients who had recently had severe hematemesis, however, and no further hemorrhage was occasioned.

CASE REPORTS AND DISCUSSION

To date, the usefulness of cytology has been most apparent when roentgenologic findings were negative or equivocal. At the University of California Hospital, we have already observed numerous cases in which cytology permitted positive diagnosis after all other diagnostic means had failed. The contribution which the papain method may make to effective surgical treatment of gastric cancer is clearly illustrated by 3 of these cases:

CASE 1. J. D., a 46 year old white male, had been under treatment for a gastric ulcer for about 18 months. One episode of hematemesis had occurred at the onset of illness, but with no further bleeding.

Because of the persistence of mild epigastric distress, the patient was admitted to San Francisco Hospital for further evaluation. A gastrointestinal x-ray film demonstrated an ulcer crater on the lesser curvature of the stomach near the pyloric antrum (Fig. 2). Although there was no roentgenologic evidence of cancer, the possibility could not be ruled out and further studies were ordered. Gastroscopic examination failed to visualize the ulcer. Gastric lavage, using the papain technique, was performed following the gastroscopic examination, however, and numerous malignant cells were seen on the stained smear. Ten days later papain lavage was repeated and malignant cells were again observed.

Because of these positive gastric smears, and the persistence of symptoms, an exploratory laparotomy was performed. An ulcer, 2 centimeters in diameter, was seen on the lesser curvature of the stomach and a subtotal gastrectomy was performed. Pathologic diagnosis of the ulcer revealed an adenocarcinoma. There were no lymph node metastases.

The patient is living and well 3½ years after surgery.

In this instance it was impossible to determine whether malignancy was coexistent with the ulcer from the beginning. It must be remembered that malignancy is a major consideration in the diagnosis of any stomach ulcer, since at least 10 per cent of such lesions will prove to be malignant eventually. Lampert found 73 cancers in a series of 550 ulcers originally believed to be benign on the basis of x-ray and other clinical studies.

CASE 2. H. K., a 67 year old Japanese male, visited his physician with a complaint of epigastric pain of 2 weeks' duration. Neither the physical examination nor x-ray studies demonstrated definite evidence of pathology, but gastric analysis revealed a low total acid value and no free acid.

Because of these laboratory findings, a papain lavage was ordered, and the presence of malignant cells was revealed. A second roentgenologic study was undertaken, and this time a questionable mass was observed in the cardiac region of the stomach (Fig. 3a and b).

On the basis of the positive gastric smear and the suggestive findings of the second x-ray examination, an exploratory laparotomy was performed. An irregular ulcerated mass, 5 centimeters in diameter, was found on the posterior wall of the stomach near the greater curvature in the cardia, about 5 centimeters distal to the esophageal orifice. A subtotal gastric resection was accomplished wherein approximately five-sixths of the stomach was removed. Histologic study of the specimen revealed an adenocarcinoma with minimal invasion of the muscularis and without lymph node metastases.

The patient is living and well, without evidence of recurrence or metastases, 3 years after surgery.

In this instance, the growth was located in an area especially difficult to visualize roentgenologically, and the only unequivocal evidence of disease was provided by the cytologic study. The size of the malignant tumor was quite remarkable in view of the short duration of the symptoms.

CASE 3. F. J., a 65 year old white female, entered the University of California Hospital on June 18, 1950, with a history of chronic epigastric distress, including loss of appetite, occasional nausea, and inability to gain weight. The symptoms were of many years' duration, and 4 years prior to entry gastric polyposis had been diagnosed by x-ray examination and confirmed by gastroscopy.

Repeated roentgenologic studies and gastroscopic examination verified the earlier diagnosis of polyposis. A routine papain lavage following the gastroscopic examination, however, revealed cells suspicious for cancer. A week after entry, therefore, a subtotal gastrectomy was performed.

Fig. 2. The diagnosis of the true nature of the lesser curvature ulcer was impossible by routine investigative methods. The presence of cancer was established by cytologic study.

The pathologic diagnosis revealed multiple small benign papillomas of the stomach, with one malignant papilloma, 2.0 centimeters in diameter. Regional lymph nodes were free of metastatic deposits.

The patient is living and well 3 years after the resection.

In this case, there was no reason to suspect cancer prior to the cytologic examination; the symptoms were of long duration and seemed to be adequately accounted for by the established diagnosis of polyposis. In view of the well known tendency of both papillomas and gastric ulcers to malignant degeneration, it would seem wise to do periodic cytologic studies on all patients known to have either abnormality.

It should be noted that in not one of these 3 cases were regional lymph nodes involved, which suggests that the lesions were in an early stage of development. It is reasonable to conclude, therefore, that like pulmonary cancers, very small gastric cancers may exfoliate diagnostic cells in great numbers.

This finding is confirmed by the series recently published by Traut and his associates. Of 414 cases studied by the papain technique as well as more usual methods, a total of 42 cases of gastric cancer were discovered. Twenty-eight of these cases were detected by the

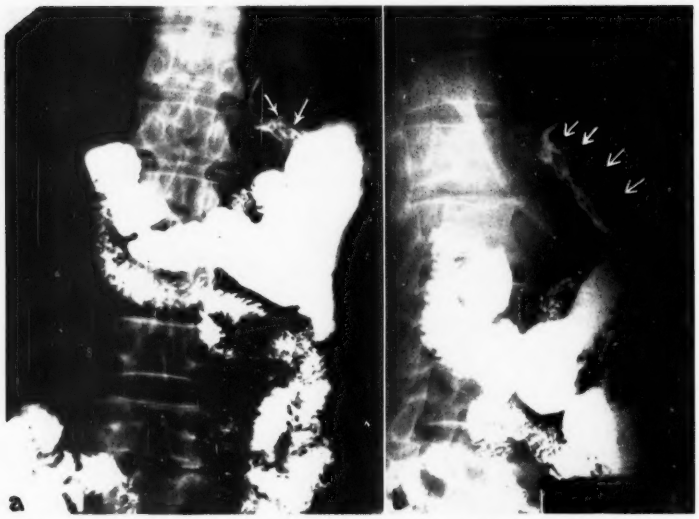

Fig. 3. The initial roentgen study of the stomach was negative. a, Note the questionable area in the cardia on the second x-ray examination following positive papain lavage. b, Cellular study afforded a definitive diagnosis to an otherwise inconclusive report.

papain method. In an additional 7 cases the diagnosis was not made because of demonstrable failure in the procedure of collecting and examining the specimens. Of the remaining 7 cases in which the cytologic diagnosis was falsely negative, one was from a case of linitis plastica (proved by subsequent surgery) with no superficial ulceration, and 5 cases involved complete or nearly complete pyloric obstruction. Only 1 case was missed for no apparent reason.

It is obvious that these statistics do not do justice to the usefulness of the papain method of cytologic study. It is diagnostically ineffective when the growth has reached an obstructive stage. Such cases, however, do not present a diagnostic problem. On the other hand, cytology has proved of greatest service in detecting small growths which are least liable to diagnosis by other methods. It is in this crucial, early stage that resection of the lesion is most apt to effect a long term cure. This fact emphasizes the value of the papain technique as a diagnostic adjunct to effective surgical treatment of gastric cancers.

The one absolute requirement of cytologic diagnosis is that final analysis be made by a pathologist thoroughly experienced in the technique. It has been necessary to develop the criteria for malignancy empirically, and as a consequence we have had a total of 7 false positive reports in well over 1,000 cases seen at the University of California laboratory. The latest instance is instructive:

CASE 4. F. H., a 73 year old white female, was first seen at the University of California Hospital in April 1949. Her chief complaint was a dull, steady, aching pain in the midepigastrium radiating across the entire upper abdomen, especially in the right upper quadrant. The pain had been present for 6 months and was accompanied by nausea but no vomiting. The initial gastrointestinal roentgenologic study demonstrated a ragged appearance on the greater curvature near the cardiac portion of the stomach. Gastroscopy revealed only atrophic gastritis, but gastric analysis demonstrated no free acid and a total acidity of only 13 units.

The patient was followed for over a year, but no change in the rugal pattern was observed until September 1950, when the irregularity was noted to be increased, and a filling defect appeared on the greater curvature (Fig. 4a, b, c). The patient was readmitted to the hospital, and on October 3 a second gastroscopic examination was performed. Again only atrophic and hypertrophic gastritis was observed, but papain lavage produced cells which were diagnosed as malignant. A repeat lavage a week later confirmed the earlier finding.

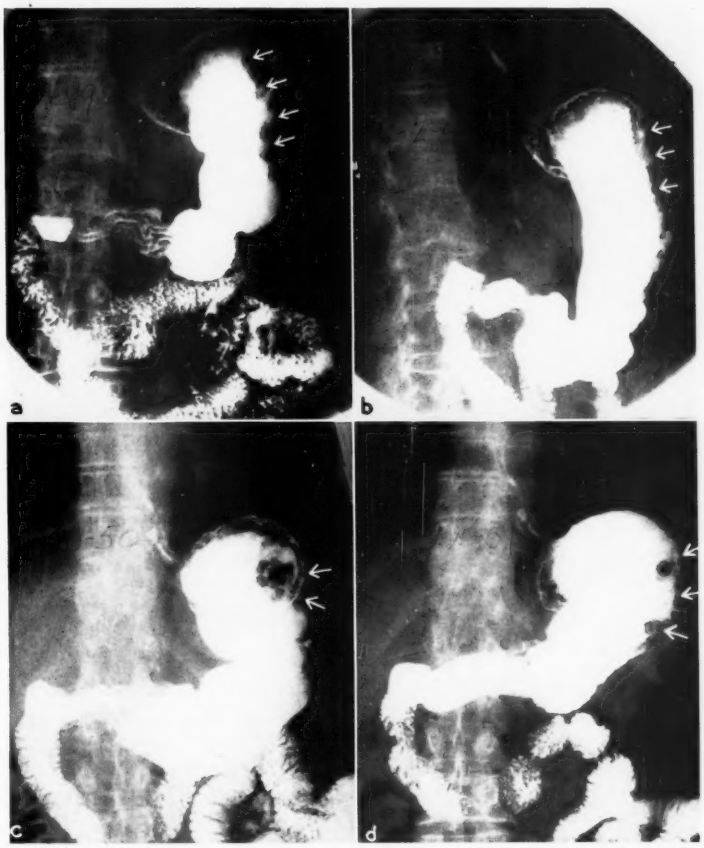

Fig. 4. Note the slight irregularity of the greater curvature near the cardia. a, The roentgen diagnosis of tumor seemed definite after several repeat studies. b, c, d, The false positive report from papain lavage resulted from the presence of bizarre cells now recognized as nonmalignant.

Symptoms persisted and in January 1951 a repeat gastrointestinal series showed the same filling defect as seen before (Fig. 4d). A third papain lavage produced a smear diagnosed as positive for malignant cells. On the basis of the patient's symptoms and the repeated positive cytologic findings, a subtotal gastric resection was performed. No palpable masses were observed, however, and a pathologic study of the area of hypertrophic gastritis on the greater curvature failed to reveal the cancer which was suspected on the basis of preoperative studies.

The patient developed a postgastrectomy obstruction, and reoperation was necessary. In June of 1951 death followed peripheral collapse.

In this case, cells regarded as malignant were bizarre, vacuolated, and hyperchromatic with apparent molding. Subsequently, similar cells seen were recognized as evidence, not of cancer, but of gastric hypertrophy.

It can reasonably be assumed that papain lavage will minimize the problem of false positive reports, as well as permit increased sensitivity. Cell relationship is well preserved by the papain method. Moreover, since a large number of cells are ordinarily present, a specimen lacking sufficient diagnostic material is quickly detected and repeat washings may be requested. Case 4 was the last false positive case encountered, and it can be hoped that this hazard will be eliminated very shortly.

SUMMARY AND CONCLUSION

A brief report of the contribution of papain lavage technique to the effectiveness of gastric cytology is presented, and 4 cases studied by this method are described. In 3 of these cases, cytologic study demonstrated the presence of cancer after other diagnostic methods had failed to yield conclusive evidence. Resection was possible in each instance, and the patients are apparently free of disease to date, from 3 years to 42 months after operation. These cases emphasize the value of cytology in detecting malignant lesions of the stomach while they are still not only resectable but in a stage in which surgical treatment may effect long term cures, rather than merely palliative results.

The fourth case illustrates the fact that the false positive report cannot yet be regarded as fully eliminated from cytologic diagnosis. However, there has been no false positive report made by the University of California laboratory for the past 2½ years, and it can be expected that further experience with this diagnostic method will make a positive cytologic diagnosis ultimately as reliable as a positive tissue biopsy.

It is suggested that a wider use of cytology as a routine method of evaluation of gastric symptoms can make a substantial contribution to the control of malignant lesions. Its use is mandatory, we believe, in the diagnosis of any gastric complaint in patients over 50 years of age.

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ELECTRICAL STIMULATION OF THE CENTRAL END OF THE VAGUS NERVE IN THE UNANESTHETIZED DOG

Method and Effects on Gastrointestinal, Respiratory, and Circulatory Systems

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THERE has long been an interest in the role of the sensory fibers of the vagus nerves located at the level of the diaphragm in the mediation of astrointestinal and cardiovascular reflexes. As early as 1769 Albrecht von Haller presented vidence that vomiting could be induced by timulation of nerves running along the anterior and posterior portions of the esophagus. ubsequent studies carried out in the anesthetized or narcotized animal have demonstrated that vomiting can be induced by electrical stimulation of the central cut end of the agus. This effect persists in the decerebrate nimal, is abolished by destruction of the medulla, and is depressed by various influences, ncluding lack of oxygen, excess of carbon dioxide, and by agents such as ether and dial. Recent experiences in man in which several deaths have occurred in association with operations involving the vagus near the cardia have prompted studies of the effect of mechanical and electrical stimulation of the central end of the vagus nerve on circulatory reflexes. Chester and his associates caused usually an elevation, but occasionally a decrease in blood pressure from electrical stimulation of the central end of the vagus along the lower esophagus in the anesthetized dog, but the effect on heart rate was inconstant. Taylor and co-workers noted a striking elevation of blood pressure from electrical stimulation of the central end of the vagus in the neck in dogs while under anesthesia. The clinical observation that abdominal distention and "gas on the stomach" may be associated with angina pectoris or changes in cardiac rhythm has from time to time directed attention to the possible role played by the afferent fibers of the vagus nerve in these circulatory phenomena. It has been suspected that a vagovagal reflex with the afferent impulses arising along the lower thoracic and on abdominal areas may account for such circulatory changes.

Our plan has been to study such reflexes under conditions free of the modifying influences of drugs or anesthesia. Therefore, a method of electrical stimulation has been worked out in which bipolar electrodes can be left in place on the central cut end of the vagus nerve. Such a study has been made in 8 dogs in whom electrical stimulation has been performed from 2 up to 10 days following electrode implantation. In all the experiments observations were made of the effect of electrical stimulation of the central end of the vagus nerve on retching and vomiting. In 3 dogs electrical stimulation of the vagus nerve was also studied for its effect on the continuous registration of heart rate, blood pressure, and respirations.

METHOD

Several techniques were tried in arriving at a satisfactory method of electrode implacement on the vagus nerve. The method which proved most suitable will be described. Our experiences with variations of this method are summarized under results.

Electrode implantation. After mongrel dogs were anesthetized with nembutal administered intravenously, a cuffed endotracheal tube was

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inserted and connected to a positive pressure apparatus supplying oxygen. The animal was placed in the right lateral position with the left side uppermost. After routine operative preparation of the skin, a standard thoracotomy incision was made, the eighth or ninth rib being resected subperiosteally for added exposure of the lower end of the esophagus and diaphragm. The left vagus nerve was isolated at a point where it disappears through the esophageal hiatus along with the esophagus and was dissected free for a distance of about 4 centimeters proximally. Care was taken not to handle the nerve except by a silk ligature passed around it. The nerve was then divided at the level of the diaphragm and its accompanying artery ligated without tying the nerve. This ligature was left long as an added convenience in fixing the two electrodes on the nerve. The electrodes were made of No. 30 fine silver wire, .010 inch in diameter, and were covered with nylon except for the distal inch. Each wire was enclosed up to the exposed areas in No. 442T vinyl tubing with an inner diameter of .039 inch. Each wire was fixed to the vagus nerve with 2 to 3 turns in spiral fashion so as not to compress the nerve by a tourniquet effect. The silk ligature, previously left long, was tied about the electrode for added fixation. Three layers of Penrose tubing, each of different size, were threaded one within the other and placed over the electrodes and the vagus nerve itself for at least 1 centimeter beyond the electrode to insure adequate insulation. A loose tie of silk was placed about the Penrose tubing proximal to the electrode (Fig. 1). The tubing containing the electrode was then brought out through the posterior angle of the incision without added fixation within the chest. In order to minimize the chances of a pneumothorax and prevent the dog from pulling at the electrodes, they were brought subcutaneously to the interscapular region at the base of the neck where 2 purse-string sutures placed about the point of exit and 2 ties enclosing the electrode within the tubing prevented entry of air into the thoracic cavity. The incision was closed with silk technique in layers. The lung was well expanded as closure was effected. A catheter placed in the incision was aspirated after the incision was airtight in case the lung did not seem satisfactorily expanded.

By dividing the purse-string sutures the electrodes and tubing could be easily withdrawn from the dog by a firm quick pull without apparent injurious effect to the unanesthetized animal. Pneumothorax was prevented by having another purse-string suture in place which could be rapidly drawn tight and tied as the tubing was pulled out.

Experimental procedure. When the blood pressure was recorded intra-arterially, the dog was placed on his back with his legs tied during the stimulations. Otherwise the animal was either standing or sitting. A model 3 C Grass stimulator was employed which delivered a monophasic square wave. The characteristics of electrical stimulation that were associated with an effective retching, respiratory, or circulatory response were as follows: 10 to 30 cycles per second, 1 to 10 milliseconds' pulse duration, and 4 to 40 volts. The duration of each stimulation was varied depending on the time of the onset of salivation, retching, vomiting, and alteration in breathing. When the effects on heart rate and blood pressure were studied, the duration of the stimulus was extended to as long as 75 seconds. Usually the time interval of the stimulus varied from 2 to 30 seconds. There was a minimal time of 60 seconds between stimulations. Motion pictures were made of the changes in breathing and of vomiting in 1 experiment. The blood pressure was recorded continuously by means of a Sanborn electromanometer with a plastic catheter in the femoral artery and the respirations with a pneumatic cuff placed around the lower thorax.

After the completion of the studies, the condition of the vagus nerve to which the electrodes were attached was determined in 3 dogs. In 3 other dogs, the electrodes were pulled off the nerve and out through the chest with the animal in the unanesthetized state.

RESULTS

Electrode implantation. Several variations of our method of electrode implantation on the vagus nerve were tried. Enclosing the two electrodes, already insulated with small flexible vinyl tubing within a heavy tubing of the

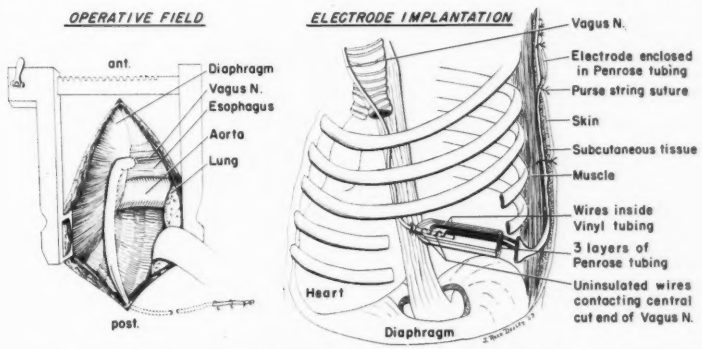

Fig. 1. Drawings showing the operative field and method of electrode implantation on the central cut end of the vagus nerve. The operative field is shown by the drawing on the left. The diagrammatic sketch on the right shows the approximate location of the part of the vagus nerve electrically stimulated, the electrode construction and the technique utilized to minimize the possibility of pneumothorax.

ıme material instead of Penrose tubing, was ›und to be unsatisfactory. This heavier tub- ıg could not be readily bent. An effective ıeans of occluding the external opening in the ıbing was not solved, nor could air be pre- ented from getting through into the pleural ıvity along the outside of this stiff tube. The ›posed end of the electrodes was first made ı the form of cylindrical cups which could ›e spread and then bent back over the nerve. With this method we failed to obtain re- ›ponses to electrical stimulation as early as he second or third postoperative day. It was elt that the inflexibility of the metal caused ischemia of the nerve as it swelled. When the external ends of the electrodes were buried underneath the skin between the scapulae, fluid collected subcutaneously about the electrodes which would become contaminated and was able to pass along the tubing into the thoracic cavity and produce empyema.

In 3 dogs in whom the Penrose tubing was used to cover the electrodes with the external ends of the electrodes being left outside the skin between the scapula, the thoracic cavity was re-explored. Large amounts of fibrin were found covering the electrodes at the attachment to the nerve. A moderate amount of fluid was present but infection was minimal or absent. Daily injections of crysticillin in a dosage of 300,000 units had been given intramuscularly each postoperative day.

Effects of electrical stimulation. Two of the 10 dogs in which electrodes were implanted along the vagus nerve expired because of a pneumothorax before any observations were made. In the remaining 8 dogs studied during the unanesthetized state, electrical stimulation of the central cut end of either or both vagus nerves at the lower third of the esophagus and below the pulmonary nervous plexus was found to cause retching, salivation, and, under certain circumstances, vomiting. Associated with these digestive tract responses were changes in respirations, slowing of heart rate, and an increase in pulse pressure. In certain instances, an intensity of electrical stimulus less than that giving rise to retching caused alterations in breathing. The intravenous administration of apomorphine simulated the digestive, respiratory, and circulatory changes produced by electrical stimulation. The intravenous administration of large doses of atropine abolished the slowing of heart rate but not the alterations in breathing and retching elicited either by apomorphine or electrical stimulation. Nembutal given intravenously in sufficient amounts to cause anesthesia abolished all responses to electrical stimulation previously obtained in the unanesthetized animal except slight alterations in breathing. The details of these results are presented under the separate headings and are summarized in Tables I and II.

TABLE I.—DATA OF EFFECT OF ELECTRICAL STIMULATION OF CENTRAL END OF VAGUS NERVE ON RETCHING OR VOMITING IN 6 UNANESTHETIZED DOGS*

No. of dog	No. days postop.	Vagus cut	Vagus stimulated	Total No. stimulations**	Data on stimulations				
					No. stimulations giving positive response	Characteristics of threshold stimuli used			Description of response
						Cycles per sec.	Pulse duration (millisec.)	Volts	
1	2	left	left	15	10	30	10	7	Salivation, retching, vomiting***
2	2	left	left	8	5	30	10	7	Salivation, retching, deep breaths, vomiting***
3	2	left	left	5	3	30	10	5–7	Salivation, retching, vomiting
Anesthetized 60 min. before with 360 mgm. nembutal i.v.	3	left	left	6	3	30	10	5–7	Salivation, retching, vomiting***
	3	left	left	6	0	30	10	7–10	No salivation, retching, or vomiting responses obtained
	5	left and right	left	4	2	30	10	7–10	Salivation, retching, vomiting***
	9								Electrodes pulled out of chest in unanesthetized animal with no adverse effects
4	2	left	left	5	3	30	10	5–7	Salivation, retching, vomiting***
5	1	left	left	7	3	30	10	4–7	Salivation, retching. No attempt to elicit vomiting
	2	left	left	8	0	30	10	4–70	No responses, presumably defect in electrodes
6	2	left	left	8	4	30	10	4–7	Salivation, retching, vomiting***
	3	left	left	13	10	30	1	6	Salivation, retching, vomiting***

*Continuous recording of respirations and intra-arterial blood pressure were not done in these experiments.
**The difference between the total number of stimulations and the number of stimulations giving a positive response included stimulations with current values less than that giving response and those giving inconsistent response.
***Vomiting was elicited by allowing the stimulation to continue for 5 to 10 seconds longer than that needed to cause retching.

Gastrointestinal responses.—Electrical stimulation of either the left or right vagus nerve in each experiment in all 8 unanesthetized dogs caused retching (Fig. 2). This was true whether or not the opposite vagus nerve had been cut. In addition, vomiting could be elicited and its presence was dependent upon whether the dog had been fed the day of the experiment and upon a slight increase in the intensity or duration of the minimal current causing retching. During electrical stimulations in which the dog was placed on his back in order to record the blood pressure from the femoral artery salivation could not be readily observed. The minimal effective parameters used to cause retching are shown in Tables I and II. It can be seen that in the unanesthetized animal retching was produced with as little as 2 milliseconds' pulse duration and 4 volts with a frequency of 10 to 30 cycles per second. The range of the minimal effective parameters of stimulation was from 1 to 10 milliseconds' pulse duration, 4 to 40 volts, and 10 to 30 cycles per second. The higher intensities of current were usually needed after the electrodes had been in place several days although this was not always the case. When the threshold intensities of current were used, retching occurred usually from 3 to 18 seconds after the beginning of the stimulus. Retching continued from 2 to 26 seconds after the end of electrical stimulation.

As shown in Tables I and II, dogs 3 and 6 were reoperated upon in order to cut and apply electrodes to the remaining intact vagus nerve. In dog 7 both vagi were cut at the initial operation. After both vagi had been severed, we continued to obtain the same retching response from electrical stimulation.

Retching in response to electrical stimulation was abolished by the intravenous injection of nembutal. After dog 3 received 6 cubic centimeters or 360 milligrams of nembutal intravenously a 30 per cent increase in voltage

TABLE II.—DATA OF EFFECT OF ELECTRICAL STIMULATION OF CENTRAL END OF VAGUS NERVE ON RETCHING, RESPIRATIONS, AND PULSE PRESSURE IN 3 UNANESTHETIZED DOGS

No. of dog	Postop. day of study	Vagus cut	Vagus stimulated	Total No. stimulations	Description of responses: Data on electrical stimulations giving responses: No. stimulations giving responses	Characteristics of threshold stimuli used: Cycles per sec.	Pulse duration (msec.)	Volts	Duration of stim. (range sec.)	Retching: Latent period (range sec.)	Retching: Duration after end of stim. (range sec.)	Respirations: Latent period (range sec.)	Respirations: Other	Circulatory: Pulse rate slowing per min. Av.	Pulse rate slowing per min. Range	Pulse pressure increase (range* mm. Hg)
6	2	left and right	right	6	2	30	10	25–30 **	8–12	5–6	2	tech.		tech.	tech.	tech.
			left	7	3	30	10	12–14	8–12	5–6	2	—	—	72	60–96	0–20
7	2	left and right	left	5	4	10	2	3–5	14–22	5–6	5–10	<2	Partial arrest with escape	100	90–114	35–65
			right	11	2	10	2	30–40	10–12	10–12	12–26	<2	Partial arrest with escape	94	88–100	30–50
					(Apomorphine 0.24 mgm. i.v.)				—	145	—	—	Slowing with escape	(144–maximal)		(85–maximal)
					(Apomorphine 0.24 mgm. i.v. repeated 6 min. later)				—	160	—	—	Slowing with escape	(120–maximal)		(75–maximal)
					(Atropine 2.0 mgm. i.v. given 10 min. later)				—	—	—	—	—	—		—
-6 min. after mgm. atropine v.		left and right	left	2	2	10	2	4–5	20	8	8–10	<2	Cessation with escape	0	0	10
					(Apomorphine 0.6 mgm. i.v. given 18 min. after atropine 2 mgm. i.v.)				—	60	—	—	Increased depth	0	0	0
8	4	left	left	9	3	30	2	7–10	12–14	7–8	4–8	2–3	Cessation or arrest with escape	16	12–24	tech.
5–210 sec. after 30 mgm. nembutal i.v.		left	left	2	2	30	2	10	23–41	16–27	15–27	13–23	Arrest with escape	tech.		tech.
0–180 sec. after additional 20 mgm. nembutal i.v.		left	left	3	3	30	2	10–20	40	0	0	<2	11–15 point rate increase per min. and decrease in amplitude	0	0	tech.
	6	left	left	6	3	10–30	2	4–5	17–30	6–18	5–8	<2	Partial arrest with escape	80	78–96 ***	tech.
12–360 sec. after 240 mgm. nembutal i.v.		left	left	2	2	10	2	5	40–41	23–25	15–18	<2–4	Increased rate and decreased depth	90	84–96	tech.
120–960 sec. after additional 120 mgm. nembutal i.v.		left	left	6	3	10	2	8–10	40–50	**** 26–29	23–24	2–4	Increased rate and decreased depth	0	0	tech.
180–360 sec. after additional 120 mgm. nembutal i.v.		left	left	2	2	10	2	8–10	58–60	0	0	3	Increased rate and decreased depth	0	0	tech.
	10	left	left	9	8	10–30	2–5	6–9	14–34	8–16	3–8 *****	2–3	Arrest with escape	36	8–78	25–55
120–480 sec. after 240 mgm. nembutal i.v.		left	left	4	2	30	2	9–20	45–60	0	0	<2–3	Decreased depth and 12–15 point rate increase per min.	0	0	0
120–360 sec. after additional nembutal 120 mgm. i.v.		left	left	2	2	30	2	20–30	70–75	0	0	2	Decreased depth and 15 point rate increase per min.	0	0	0

*With increase in pulse pressure there was an elevation of systolic pressure ranging from 12 to approximately 50 mm. Hg. The diastolic pressure usually decreased but might also remain unchanged or increase.

**These were electrical stimulations at 10 volts which was associated with a 25 mm. Hg. rise in systolic pressure and a 20 mm. increase in diastolic pressure.

***There was return of heart rate toward prestimulation level before end of retching during one of the stimulations.

****Retching responses were not associated with decrease in heart rate; the accompanying respiratory excursions were both decreased and increased during retching.

*****Dog, however, retched in 5 seconds after one stimulus was turned off in which 20 volts were used for 60 seconds.

tech., Technical difficulty in recording.

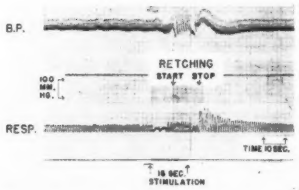

Fig. 2. Recording of changes in blood pressure, heart rate, and respirations during electrical stimulation of the central end of the left vagus nerve in the unanesthetized dog (No. 7) and their relationship to retching elicited by this stimulus. Within 1 second after the beginning of electrical stimulation there was an almost complete cessation of respiration. About 6 seconds later retching started simultaneously with increased respiratory excursions and with a striking slowing of heart rate from 150 to 42 beats per minute and increase in pulse pressure from 65 to 135 millimeters of mercury. Retching continued for 5 seconds after the end of electrical stimulation.

caused no retching, salivation, or vomiting.[1] Dog 8 was studied on 3 different occasions following intravenous nembutal administration. Each time repeated electrical stimulation with the same or moderately greater intensities of current causing retching before drug administration produced retching for as long as 90 to 480 seconds after 240 milligrams of nembutal was given. On 2 occasions an additional administration of 120 milligrams of the drug abolished the retching response to an increase in the voltage strength of stimulation of from 100 to 230 per cent (Fig. 3). On 1 occasion retching was obtained by a 50 per cent increase in voltage after the injection of a total of 360 milligrams of nembutal. An additional 120 milligrams of the drug then abolished retching to the same amount of electrical stimulation (Table II). Retching continued to be obtained by electrical stimulation after the administration of as much as 2 milligrams of atropine given intravenously (Fig. 4). The retching response elicited by the intravenous administration of apomorphine will be discussed later (Fig. 5).

Respiratory responses.—The breathing pattern was recorded in detail in dogs No. 7 and 8 by means of a pneumatic cuff placed around the lower thorax. With this technique we found that in the unanesthetized animal changes in breathing always accompanied retching (Fig. 2). Immediately or within 1 or 2 seconds of the beginning of electrical stimulation there was almost always a decrease in amplitude and rate of chest movements with an escape to increased amplitude of respiratory movements simultaneous with the onset of retching. Rarely a slight diminution in amplitude and rate of breathing was elicited by electrical stimulation with intensities of current just below those giving rise to retching. It was of interest that, when the retching response was abolished by nembutal, electrical stimulation was commonly associated with a slight to moderate decrease in amplitude and a 12 to 15 point increase in rate of chest movements per minute (Fig. 3). The administration of 2 milligrams of atropine intravenously had no effect on the type of chest movements associated with retching.

Circulatory responses.—The circulatory changes obtained during the electrical stimulation consisted of a slowing of heart rate usually with an increase in pulse pressure and only occurred in association with retching or vomiting (Fig. 2). The intensities of current used to elicit these circulatory responses were only the minimal values needed to produce retching (Table II). With these intensities of current the heart rate was decreased on an average of 70 beats per minute during effective stimulation with the decline in heart rate ranging from 12 to 114 beats per minute. The pulse pressure increase was from zero to 65 millimeters of mercury. The systolic pressure rose from 12 to 50 millimeters of mercury. The diastolic pressure remained unchanged, decreased as much as 35 millimeters of mercury, or increased up to 15 millimeters of mercury. In 2 experiments technical difficulties in recording made it impossible to determine the quantitative change in pulse pressure, systolic or diastolic pressure.

In dog 6, electrical stimulation of the central end of the cut vagus nerve with 1 or 2 volts less than that giving rise to retching caused on 2 occasions a slow progressive increase in blood pressure with a maximal systolic elevation of 25 millimeters of mercury and 20 millimeters of mercury rise in diastolic pressure. This response was accompanied by a deep forceful respiration but with no change

[1]Our dogs were not regularly weighed. Therefore, the dosages of drugs employed cannot be stated in kilograms per body weight.

in heart rate. This was the only instance in which an elevation of blood pressure occurred in the absence of retching. As shown in Figure 3, electrical stimulation following the intravenous administration of 360 milligrams of nembutal was not associated with change in heart rate, systolic and diastolic, or pulse pressure.

When electrical stimulation of the nerve was repeated at from 4 to 6 minutes after the intravenous administration of 2.0 milligrams of atropine, the same parameters or an increase of 1 volt caused retching and breathing changes but the effect was associated with no change in heart rate (Fig. 4). There was, however, a marked elevation of both systolic and diastolic blood pressure, the maximal systolic rise being 70 millimeters of mercury and the maximal diastolic rise, 60 millimeters of mercury. Atropine, apparently by abolishing motor vagal impulses to the heart, prevented the diminution of heart rate previously observed when no medication had been given. As shown in Figure 5, apomorphine, 0.24 milligram, given intravenously to the unanesthetized dog was followed in 145 seconds by an episode of retching which lasted about 45 seconds. This was followed in 34 seconds by another episode of retching which lasted about 20 seconds. Both episodes were associated with a marked slowing of heart rate from 160 beats to from 36 to 54 beats per minute. The pulse pressure at the same time increased from 65 to about 150 millimeters of mercury. It was possible, therefore, with this emetic agent to mimic both the retching and associated circulatory responses obtained by central vagal stimulation. The tracing to the right in Figure 5 shows that retching which was again induced by the intravenous injection of 0.6 milligram of apomorphine caused more retching but no associated heart rate change when the animal was still atropinized with 2 milligrams of the drug given intravenously 18 minutes earlier. We were not certain whether the blood pressure change noted in this tracing represented a true response or was due to a technical factor in the recording.

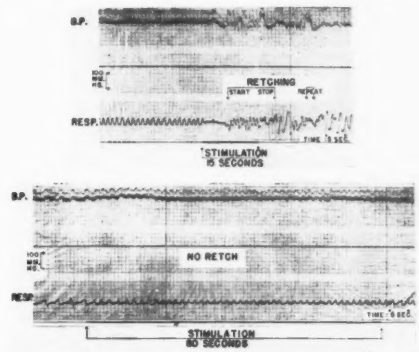

Fig. 3. Tracings show that intravenous nembutal administration in amounts sufficient to anesthetize dog (No. 8) abolished retching previously obtained in response to electrical stimulation of the central end of the vagus nerve in the animal when unanesthetized. The tracing above shows retching and slowing of heart rate in response to electrical stimulation of the central end of the left vagus nerve in dog (No. 8). Only the left vagus nerve had been cut. After the administration of 360 milligrams of nembutal intravenously an elevation from 9 to 30 volts or greater than 200 per cent increase caused no retching, no change in heart rate, but an increase in rate of breathing from 24 to 36 per minute with a dimunition in the amplitude of respiratory excursions. Nembutal (240 mgm.) was given 18 minutes before and an additional 120 milligrams 6 minutes before the electrical stimulation shown in lower tracing.

DISCUSSION

A technique has been described and the results presented for electrical stimulation of the central cut end of the vagus nerves along the distal portion of the esophagus in the unanesthetized dog. Responses were obtained as long as 10 days after operation without the need of increasing the intensity of current. The experimental data show in each animal that electrical stimulation of the central end of the left vagus nerve was associated with retching, increased depth of breathing, and, frequently, salivation and vomiting. This response was obtained whether or not the right vagus nerve was intact and could also be elicited from electrical stimulation of the central cut end of the right vagus nerve. These findings confirm the results of others who have shown that the sensory vagal stimulation at the level of the esophagus will give rise to vomiting in the anesthetized animal. Lack of detail in the description of the electrical stimulation technique used by others made it impossible to state whether the same current was needed by us to elicit vomiting as that used by others in the anesthetized animals. In our studies we know that a 130 per cent increase in

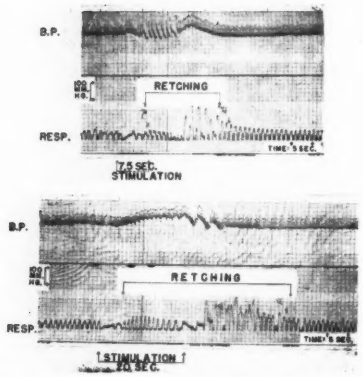

Fig. 4. Chart shows that 2.0 milligrams of atropine intravenously abolishes the slowing of heart rate associated with retching when the central end of the left vagus nerve was electrically stimulated in the unanesthetized dog (No. 7). The tracing above shows a slowing of the heart rate from 168 to 60 beats per minute during and just following electrical stimulation. The tracing below made 6 minutes later or 4 minutes after the administration of 2.0 milligrams of atropine intravenously caused no change in heart rate but the retching produced was associated with a striking increase in systolic and diastolic blood pressure. In this dog both vagi had been cut.

voltage did not cause vomiting in dog 8 when under light nembutal anesthesia as compared to what was needed with the animal in the unanesthetized state. So far as we are aware, the only report of a study of the effect of stimulation of the central end of the vagus nerve on vomiting in the unanesthetized animal is that of Anokhin. After anastomosing the central end of the vagus nerve to afferent fibers of the radial nerve innervating the dog's front paw, he found that light stroking of the skin of the paw caused the animal to cough. With more intense stroking the animal vomited. In a review of his experiences with peripheral nerve surgery Foerster makes several comments concerning the relationship of the vagus nerve to nausea and vomiting in man. He has observed that intracranial mechanical stimulation of the vagus nerve caused nausea and vomiting but no pain. Electrical stimulation of the vagus root (presumably in the intracranial cavity), produced such striking phenomena that he felt this procedure should not be attempted in man. Finally he noted that stimulation of the central end of the vagus nerve above the cardia produces nausea and vomiting but no pain. The details about the location and the amount of electrical stimulation used are not stated. Our ability to produce vomiting with both vagi cut makes it clear that this reflex can be elicited without the participation of the efferent vagal fibers going to the gastrointestinal tract.

The only clear-cut circulatory responses elicited by electrical stimulation of the central cut end of the vagus nerve in the unanesthetized animal was a slowing of heart rate and increase in pulse pressure. This effect was not produced unless retching occurred. Since the same circulatory effect was induced by retching due to the apomorphine administration and could be abolished by the injection of large doses of atropine, the mechanism appeared to be associated with the act of retching and motor vagal activity. The changes in respirations and intra-abdominal and intrathoracic pressure associated with retching in themselves did not give this effect. It is probable that the medulla with its vagal nuclei plays a crucial role both in the act of retching and vomiting and slowing of heart rate. Destruction of a region of the medulla near the motor nucleus of the vagus and respiratory center is said to prevent vomiting. Apomorphine, which likewise produced retching and vomiting with slowing of heart rate, is said to act on the medulla. The gag reflex, frequently successful in slowing the heart rate in patients with paroxysmal auricular tachycardia, probably also acts through vagal nuclei in the medulla. We did not carry out adequate hemodynamic studies to elucidate the mechanism of the increase in pulse pressure noted during slowing of the heart rate at the time of retching. It would seem likely that it was due to an increase in stroke volume secondary to an increased venous return of blood to the heart. The lengthened interval between heart beats would allow added time for the intravascular pressure to dissipate itself giving a lowered diastolic pressure. In the unanesthetized, nonmedicated dog we observed an elevation of both systolic and diastolic blood pressure during only two stimulations which was in dog 6. This blood pressure rise was accompanied by an increase in depth of breathing, but without retching. Our failure

to obtain the hypertensive effects reported by Taylor and his associates in the anesthetized dog may have been due to a number of factors: The duration of the stimulation in our studies was not over 75 seconds in the absence of a retching response. If retching occurred, we terminated the electrical stimulus in from 3 to 20 seconds. Taylor and his associates obtained the initial elevation of blood pressure after a 2 to 6 minute latent period. These workers, moreover, were working with the anesthetized animal, stimulated the vagus nerve in the neck, and employed a different type of electrical stimulus. We did find, however, that when dog 8 had been anesthetized with 360 milligrams of nembutal or 28 milligrams per kilogram of body weight that a 230 per cent increase in voltage greater than that needed to cause retching when the animal was unanesthetized caused no change in systolic or diastolic blood pressure (Fig. 3).

The association of salivation, retching, and vomiting with electrical stimulation of the afferent vagal fibers enables us to raise certain speculations concerning the types of symptoms that might be expected in circulatory or gastrointestinal reflexes involving such fibers. If circulatory or other changes occur due to stimuli travelling over afferent vagal fibers arising in the digestive tract or from other areas in the abdomen, it is reasonable to infer on the basis of these findings that such reflex activity might be associated with retching or vomiting.

From time to time the question has arisen whether the vagus nerves conduct pain from the digestive tract. Moore and his associates found that the same amount of balloon distention was required to produce pain from the duodenum after as compared to before transdiaphragmatic resection of the vagus nerves in patients with peptic ulcer. As pain is a subjective phenomenon, there was no way of adequately evaluating this symptom in our unanesthetized dogs. It was of interest, however, that at no time did the animals bark, jump, or whine during electrical stimulation of the vagus nerves. This was in contrast to sudden snapping and jumping away noted when 2 electrodes, left beneath the skin in the back in 1 animal, were electrically stimulated. This finding would lend support to the observations of Foerster in man which have been mentioned.

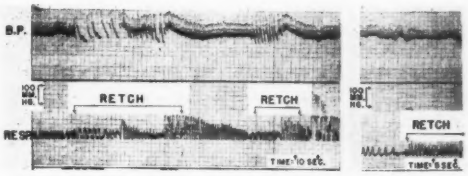

Fig. 5. Tracings show slowing of heart rate and increase in pulse pressure associated with retching induced by intravenous apomorphine injection and abolition of circulatory effects by 2.0 milligrams of atropine. The retching response shown in the tracing on the left occurred in the unanesthetized dog (No. 8) 145 seconds after the administration of 0.2 milligrams of apomorphine intravenously with a repeat effect occurring 34 seconds later. The marked decrease in heart rate and increase in pulse pressure obtained was abolished when apomorphine again induced retching, this time in the atropinized dog (lower tracing).

SUMMARY

1. A method for electrical stimulation of the central end of the cut vagus nerve located just above the cardia in the unanesthetized dog has been described. The results of electrical stimulation on respirations, retching, vomiting, heart rate, and blood pressure in 8 dogs have been presented.

2. Electrical stimulation produced changes in breathing, retching, and, under certain conditions, vomiting. Retching or vomiting was associated with slowing of the heart rate and an increase in pulse pressure. This response was obtained from electrical stimulation of either vagus nerve and persisted when both vagus nerves had been cut.

3. The intravenous administration of apomorphine simulated the effects of electrical stimulation of the central end of the vagus with respect to retching, slowing of heart rate, and increase in pulse pressure.

4. The intravenous administration of large doses of atropine abolished the slowing of heart rate and increase in pulse pressure in response to electrical stimulation or apomorphine administration but not the retching or respiratory effects.

5. The intravenous administration of nembutal in sufficient doses to cause anesthesia abolished the retching and circulatory effects of electrical stimulation of the vagus nerve.

Changes in breathing were elicited, but they were of a different type from that noted when only electrical stimulation was employed.

6. The possible importance of these findings in the understanding of circulatory reflexes arising over the vagus nerves from the gastrointestinal tract is discussed.

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INTRAHEPATIC CHOLANGIOJEJUNOSTOMY FOR BILIARY OBSTRUCTION

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AN OPERATIVE procedure was described in 1948 (7) which was intended for use in those cases of extensive obstruction of the common ile duct or common hepatic duct in which the sual methods of biliary reconstruction had roved inadequate. The procedure, descripvely named intrahepatic cholangiojejunosmy, consists of anastomosing one of the ajor intrahepatic biliary ducts to the jenum following partial resection of the left be of the liver.

Application of this surgical principle has en reported in 18 patients (Table I). In of these cases, the operation was employed alliatively to relieve primary and secondary bstruction of the extrahepatic biliary tree hich was caused by advanced malignant isease. All but 2 reports have appeared in ne American literature. A single case was ported from France by Paschoud and his ssociates. The details of an additional case ere made known to us by personal comunication with Beal.

In 1951, Dogliotti described a case in which he was required to resect a portion of the left lobe of the liver and anastomose a left intrahepatic duct to the stomach in order to establish biliary-enteric continuity; he disclaims any knowledge at the time of the principle described by Longmire and Sanford in 1948.

Although indications for the operation have differed somewhat in the hands of the various authors who have employed it, most have been agreed that under certain circumstances when other procedures have failed and little or no common hepatic duct is available for the more recognized methods of re-establishing biliary-enteric continuity, intrahepatic cholangiojejunostomy has found a definite place in the armamentarium of the general surgeon. Waddell and Burbank have ventured that "... as more experience accumulates, the procedure may be more widely applicable than is believed at present."

The purpose of this paper is to present our experience with 5 additional cases in which intrahepatic cholangiojejunostomy was employed, and to review our present concept of the operation, its indications, contraindications, modifications, and results. Four of the 5 patients herein reported were operated upon by one of us (W.P.L.) and the fifth patient (Case 3) was seen in consultation following the employment of this procedure by G. A. Falkner and J. C. Lyman.

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CASE REPORTS

CASE 1. A 54 year old Caucasian woman was admitted to the hospital on December 6, 1949 because of a 3 year history of persistent jaundice, dark urine, light stools, intermittent episodes of chills and fever and a chronic draining right upper abdominal external biliary fistula.

In November 1946, she had noted the gradual onset of nausea and upper abdominal distress followed 2 months later by the sudden appearance of jaundice, light stools, dark urine, and pruritis. In January, 1947, she was operated upon and a cholecystostomy was performed. A month later, she underwent a cholecystectomy and choledochostomy because of recurrent episodes of cholangitis and increasing jaundice. One year later she was operated upon again for persistent jaundice and on this occasion the common duct was explored through the duodenum. A catheter was left in the duct and brought out through the duodenum and anterior abdominal wall. An external biliary fistula subsequently drained in the right upper abdomen and when this became obstructed, symptoms of cholangitis ensued.

In December, 1949 she was referred to one of us (W.P.L.) for consideration of further surgery. At this time her liver and spleen were moderately enlarged and the biliary fistula was draining freely. The laboratory studies revealed a moderate degree

TABLE I.—INTRAHEPATIC CHOLANGIOJEJUNOSTOMY, CHRONOLOGICAL TABULATION OF CASES REPORTED TO DATE

Author	No. of cases	Nature of obstruction	Remarks
Longmire and Sanford (7)	1	Benign	Follow-up 2 years: greatly improved; adequate biliary drainage but had intermittent difficulties related to biliary tract
Sanders	1	Benign	Follow-up 6 months: greatly improved; 20 pound weight gain; normal stools; still slightly icteric
Wilson and Gillespie	1	Benign	Follow-up 18 months: greatly improved; stools normal; able to work almost continuously; residual mild hepatitis
Longmire and Sanford (8)	3	Benign	1 patient entirely well 11½ months after operation
			1 patient with 13 month follow-up greatly improved, but still had intermittent difficulties with biliary tract
			1 patient expired 3 months postoperatively with homologous serum hepatitis; was completely recovered and entirely well at time of onset of fatal illness
Massie	1	Benign	5 months follow-up: had 1 episode postoperatively of cholangitis with jaundice and acholic stools; recovered
Cole, Ireneus, and Reynolds	1	Benign	Stricture developed "a few months later"
Hay, Waldron, and Heard	1	Benign	7 month follow-up: markedly improved; jaundice receded; patient gained in weight and strength
Paschoud	1	Benign	10 month follow-up: patient seems to be well
Sawyer	4	Malignant	All expired 10 to 60 days postoperatively; 3 were relieved of jaundice and pruritis after operation
	1	Benign	21 month follow-up: patient was in excellent nutritional status and had regained normal weight
Waddell and Burbank	1	Malignant	Patient lived 13 months after operation; for 8 months was free of jaundice, but did have bouts of cholangitis
Hanson and McCullock	1	Benign	Patient has been symptom free for 2½ years following operation
Beal*	1	Malignant	Lived about 5 weeks after operation; jaundice did not recede before death although there was evidence of biliary drainage
Total—18 patients: 12 benign, 6 malignant obstruction			
Lippman and Longmire (present series)	5	Benign	1 patient lived 13 months after operation; biliary drainage intermittent
			1 patient followed 31 months: no evidence of biliary obstruction or cholangitis
			1 patient followed 40 months: evidence of biliary drainage from both lobes of liver but stools intermittently clay colored and jaundice persists; no cholangitis
			1 patient expired on 12th postoperative day of ruptured esophageal varix
			1 patient entirely well for 18 months
Total to date—23 patients: 17 benign, 6 malignant obstruction			

*Has not appeared in the literature.

of impairment of liver function and evidence of extrahepatic biliary obstruction. An icterus index was 77 units and there was no urobilinogen in the urine. The patient was operated upon December 9, 1949 and a partial left hepatectomy and intrahepatic cholangiojejunostomy were performed. The isolated left intrahepatic duct admitted a No. 14 French catheter through which a cholangiogram was taken at the operating table (Fig. 1). The intrahepatic biliary system was visualized in this manner throughout the right and left lobes of the liver and none of the dye was noted to escape from the external biliary fistula. The pathologist's report on the excised wedge of tissue was: biliary cirrhosis with subacute and chronic pericholangitis.

Postoperatively, the patient's course was satisfactory except for persistent periodic drainage through the external biliary fistula. The degree of jaundice receded promptly by laboratory studies but the deeply stained tissues retained their color with little change. An icterus index was recorded as 25 units on the fifth postoperative day. When she was discharged on her twenty-fourth postoperative day, there was free drainage through the fistula and only minimal amounts of bile in the stool. It was advised that the external fistula be closed surgically

n a month if it had not closed spontaneously within hat period.

Three months after operation, the patient's re-erring physician was required to operate upon her gain because of a mechanical small bowel obstruc-ion. She continued to drain intermittently through he biliary fistula and her stools remained periodical-y acholic to dark brown. The patient's condition eteriorated rapidly and she expired a little more han 1 year following the establishment of the holangiojejunostomy. An autopsy was not per-itted.

This woman had 3 operative procedures on he extrahepatic biliary system over a period f approximately 3 years. At the end of that me she had a persistent external biliary stula and impairment of liver function was oderately severe. An intrahepatic cholangio-junostomy was performed in December 949. Intermittent drainage from the biliary stula persisted until her death 13 months ter.

Our experience with this case has caused us question the advisability of performing an trahepatic cholangiojejunostomy under ese circumstances. The persistence of the xternal fistula in the presence of an adequate nternal biliary-enteric anastomosis which rained both lobes is not entirely understood. he formation of excessive scar tissue along he tract or possibly the presence of some oreign substance such as nonabsorbable su-ure material may have been responsible. In ny case, it is our impression, at least at this writing, that if an externally draining biliary istula exists, it would be wiser to approach he problem through the right upper quadrant and attempt to correct the cause of the fistula irst and then to establish biliary flow in the manner most befitting the circumstances.

CASE 2. A 27 year old Caucasian man was admitted to the hospital on October 10, 1950 with a history of having noted dark urine for 1 month and jaundice for 1 week prior to admission.

He had first been operated upon in September 1947 because of recurrent episodes of epigastric pain for over a year. Seven days postoperatively he became jaundiced, and on his eighth postoperative day he noted the sudden onset of severe abdominal pain. An emergency laparotomy revealed a rupture of the common bile duct and bile peritonitis. A ligature was said to have been seen around the common bile duct distal to the point of rupture. The peritoneal cavity was drained at this time, but

Fig. 1. Case 1. Operative cholangiogram. The entire intrahepatic biliary system is visualized.

shortly thereafter he was reoperated upon and a choledochoduodenostomy was performed. About 2 months later it was necessary to refashion the choledochoduodenostomy over a catheter which was brought through the anterior abdominal wall. Fourteen months later the patient was re-explored because of signs of intermittent biliary obstruction and a Roux Y choledochojejunostomy was performed. It was not until 2 years later that symptoms of biliary obstruction recurred and at this time, one of us (W.P.L.) was asked to see the patient regarding the possibility of further surgical intervention.

With the exception of mild icterus, the only significant finding was an enlarged liver, palpable 3 to 5 centimeters below the right costal margin. The laboratory studies revealed relatively normal liver function and markedly fluctuating jaundice. A partial left hepatectomy and intrahepatic cholangiojejunostomy were performed on January 8, 1951. A cholangiogram was made at the operating table through the exposed intrahepatic duct and the biliary system in both lobes was well visualized (Fig. 2). The patient's postoperative course was uneventful. His jaundice faded promptly. The pathologist reported that the histologic pattern of the wedge of liver tissue removed at operation was compatible with early biliary cirrhosis. The patient was discharged on his twenty-first postoperative day.

He was readmitted to the hospital on 2 subsequent occasions complaining of periodic episodes of

Fig. 2. Case 2. Operative cholangiogram. Both right and left major intrahepatic ducts are demonstrated.

dull epigastric pain, nausea, and vomiting. On each occasion he presented no evidence of biliary obstruction. A severe and extensive hemorrhagic gastritis was observed gastroscopically in January 1952. An extensive psychiatric workup also performed at this time resulted in a diagnosis of "somatization reaction" for which he was placed under psychiatric care. When discharged in June 1952, about 18 months after the cholangiojejunostomy had been established, no evidence of biliary disturbance could be elicited although the patient continued to complain about his "stomach and bowels."

He was last seen in August 1953, 31 months after operation. He appeared to be well nourished and physically fit. He denied any symptoms suggestive of biliary tract disease, although he continued to complain of episodes of dull epigastric pain, nausea, vomiting, and constipation. Further questioning elicited the fact that these complaints are very similar to those which the patient had had for at least 1 year prior to his original operation in September 1947. On physical examination, his skin and scleras were clear, his liver edge was no longer palpable.

This patient underwent 5 operative procedures on his extrahepatic biliary system during a period of 17 months. Two years later a partial left hepatectomy and intrahepatic cholangiojejunostomy were performed. This procedure was selected in order to avoid the extensive scar tissue and distortion of anatomy in the right upper abdomen and because of the previous repeated failure to establish prolonged biliary flow by other operations in the right upper quadrant.

Unfortunately it is rather difficult to evaluate the final result in this case because of the profound psychoneurosis which complicates the picture. Despite the numerous complaints referable to his intestinal tract, the patient has presented no objective evidence of biliary obstruction since his last operation in January 1951. His symptoms are probably explained by psychoneurosis, chronic pancreatitis, or duodenal ulcer in that order of probability.

Case 3. A 45 year old Caucasian woman was first seen by one of us (W.P.L.) on April 30, 1951, because of complications apparently arising from a persistent obstructive jaundice of varying degree over a period of about 9 years. The patient had had a cholecystectomy and choledochostomy in August, 1942 and 6 months later developed intermittent jaundice. A plastic reconstruction of the common bile duct was attempted in September 1943, following which the patient became persistently jaundiced. She remained jaundiced and intermittently febrile until January 1948 when a third procedure, hepaticojejunostomy, was performed. Although some degree of improvement followed, a mild jaundice persisted.

The patient's condition continued to deteriorate so that in February 1950, a partial left hepatectomy and intrahepatic cholangiojejunostomy were performed. The surgeon states that it was not possible, because of previous procedures, to defunctionalize the loop of bowel which was brought up to the liver; thus, the biliary-enteric anastomosis was necessarily placed directly in the bowel stream.

Postoperatively, the patient's jaundice receded partially and she had no pruritis, fever, or chills. However, the flow of bile was intermittent and, although her appetite was good, she was steadily losing weight. Pain in her back, legs, and hips was her chief complaint. When she was seen in April 1951 the patient presented evidence of marked weight loss, moderate jaundice, a markedly enlarged liver (particularly the right lobe), mild edema of both feet, difficulty with ambulation, suggestion of right foot drop and kyphosis and rigidity of the back. A laboratory study revealed normal serum calcium and phosphorous values, and an elevated alkaline phosphatase. Roentgenograms showed multiple fractures of the ribs, fracture of the first lumbar vertebra, and generalized osteoporosis. Operation was advised, the intention being to perform a partial *right* hepatectomy and intrahepatic cholangio-

ejunostomy. It was thought that the right lobe as inadequately drained by the procedure previously done on the left side. The patient refused to operated upon at this time and returned to her me in another state.

She returned a year later, apparently willing to ndergo the suggested operation. Her appetite was od but she had not gained any weight. Her jaunce was stationary. The liver was still very large d somewhat tender. Laboratory examination vealed only a moderate degree of liver damage. total serum bilirubin was 8.40 milligrams per cent th a 76 per cent prompt direct reaction. An per gastrointestinal series revealed moderate ricosities throughout the lower portion of the phagus and a rather unexpected cholangiogram ich was produced by the entry of the thin barium o the old left intrahepatic cholangiojejunostomy ig. 3). This fortuitous discovery revealed an oute of the entire intrahepatic biliary tree and demonated to our satisfaction that the right, as well as left lobe, was draining sufficiently through the side to obviate the necessity for further surgical ervention. The patient was discharged on a medi- regimen very similar to that which she had been lowing for many years.

This woman had 3 operations for biliary ct disease during the years 1942 to 1949. wo of these procedures were designed to reve obstructive symptoms, but were unsucssful. An intrahepatic cholangiojejunostomy as employed after 8 years of periodic difulty. Since that time, the patient has d no further episodes of cholangitis. Howver, her jaundice has persisted and she is nable to gain weight. Although drainage of ile is not complete there is sufficient evidence that it occurs from both lobes to warant no further surgical intervention. It is pparent that the degree of hepatic injury incurred prior to establishment of biliary flow is of such a degree that biliary cirrhosis and borderline hepatic reserve limit the result to be expected in any case.

The advanced osteoporosis seen in this patient is not explained. Its relationship to faulty absorption of vitamin D or to chronic liver damage is suggestive. It does not seem progressive under symptomatic management.

The inadvertent cholangiogram obtained by an upper gastrointestinal barium study reveals the ease with which the bowel content may enter the intrahepatic biliary tract unless the biliary-enteric anastomosis is placed in a defunctionalized loop.

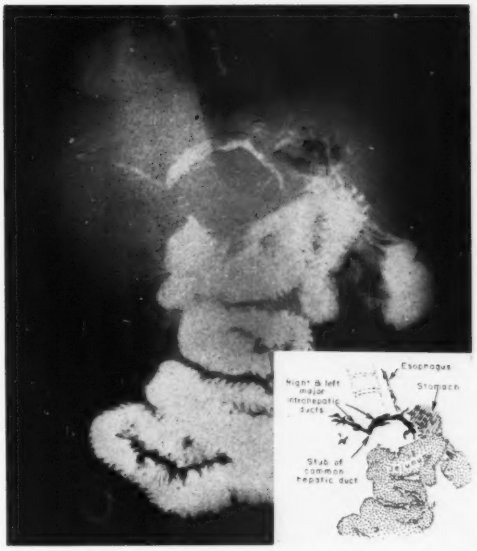

Fig. 3. Case 3. Upper gastrointestinal barium study. Note that the thin barium has entered the cholangiojejunal anastomosis and outlined both the left and right major intrahepatic ducts.

CASE 4. A 34 year old Caucasian woman was admitted to the hospital on October 9, 1951 because of progressive jaundice, ascites, weakness, clay colored stools, dark urine, severe headache, and epistaxis. The patient's pertinent past history began in March 1944, when she underwent a cholecystectomy for chronic cholecystitis and cholelithiasis. Two weeks postoperatively, she noted the onset of dark urine, light colored stools, and jaundice. Three months later, a choledochoduodenostomy was performed, following which there was a short period of improvement.

In March 1945, it was necessary to re-explore the patient for recurrence of biliary obstruction and a hepaticoduodenostomy was performed over a vitallium tube. The prosthesis passed per rectum 5 months later and biliary obstruction again intervened. In March 1946, the hepaticoduodenostomy was taken down and a hepaticocholedochostomy performed over a T tube. The T tube was removed 8 months later because of obstruction by debris. For the next 3 years, her course was characterized by periodic episodes of cholangitis following each of which the jaundice appeared to deepen.

In January 1950, the patient suffered her first of several attacks of upper gastrointestinal hemorrhage. In June 1951 she developed ascites and peripheral edema, and in October 1951 she was hospitalized because of progressive deterioration. It was under these conditions that one of us (W.P.L.) was asked to see the patient for consideration of further sur-

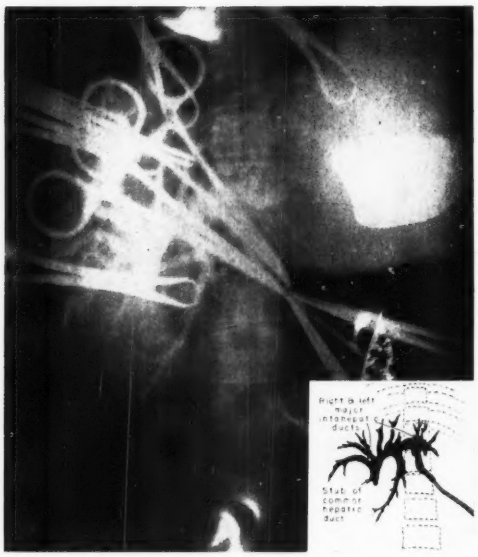

Fig. 4. Case 4. Operative cholangiogram. Entire intrahepatic biliary tree is visualized. Note large duct probably draining right lobe entering the left main intrahepatic duct.

gical intervention. At this time, her liver and spleen were both enlarged and she was markedly icteric. Her laboratory examination revealed moderate liver impairment and her icterus index ranged between 117 and 151 units. Roentgenograms had shown that there were extensive esophageal varices.

A partial left hepatectomy and intrahepatic cholangiojejunostomy were performed on November 27, 1951. A cholangiogram made through the exposed left hepatic duct, which admitted a No. 14 French catheter, demonstrated the entire intrahepatic biliary tree (Fig. 4). The patient's response to operation was satisfactory. Bile was seen in the gastric drainage on the second postoperative day and by the fourth postoperative day the patient's urine was becoming clear and the stools dark. The patient was ambulatory and gaining rapidly when, suddenly, on her twelfth postoperative day she became weak, confused, and progressively comatose. She expired on the following day. A serum nonprotein nitrogen was 174 milligrams per cent. An autopsy revealed extensive esophageal varices from which a fatal hemorrhage had apparently occurred, marked biliary cirrhosis, acute cholangitis, and extensive scarring and obliteration of the extrahepatic biliary tree. The cholangiojejunal anastomosis was found to be intact and appeared to have functioned satisfactorily.

This woman was operated upon four times over a 2 year period, the last three times representing attempts to establish biliary-enteric continuity following her original operation—a cholecystectomy in 1944. Her course from 1946 to 1951 was characterized by periodic episodes of cholangitis and finally biliary cirrhosis, portal hypertension, and hemorrhage from esophageal varices.

The question of performing a portacaval anastomosis prior to the cholangiojejunostomy or possibly a splenorenal shunt at the same time was seriously considered in this case. The decision to establish adequate biliary drainage first was based on the supposition that further hepatic damage would be lessened and possibly the necessity for a shunting operation would be obviated. The fact that the patient succumbed to a complication of her portal hypertension, we feel, is not necessarily incompatible with this reasoning. Each case must be considered on its own merits and, by and large, the performance of two separate procedures of this magnitude in a patient with such poor visceral reserve would probably represent a greater threat to life than that which exists from the complication which occurred in this case.

CASE 5. A 55 year old Caucasian woman was admitted to the hospital on December 26, 1951 with a 5 month history of clay colored stools and dark urine.

In 1945 she had had a cholecystectomy following a 2 year history of gallbladder disease and gallstones. There had been no further difficulty until 1948 at which time the patient noted the onset of periodic attacks of right upper quadrant abdominal pain associated with severe chills and fever, nausea and vomiting, and clay colored stools.

She was explored in February, 1951 and a diagnosis of obliterative cholangitis was made. It had been possible, however, to place a very small catheter into the duct and bile drained fairly well through this until the tube came out spontaneously 3 weeks later. Bile continued to drain through the fistulous tract for the succeeding 3 months and then stopped. The patient then became progressively jaundiced and passed clay colored stools.

She was referred to one of us (W.P.L.) in December, 1951. She had lost 45 pounds in weight, her appetite was poor, and ankle edema was evident. An enlarged firm liver was palpable 7 centimeters below the right costal margin. Although her obstruction was complete, the liver function tests were essentially normal. An icterus index was 40 units. On December 28, 1051 a partial left hepatectomy and intrahepatic cholangiojejunostomy were performed. A large left intrahepatic duct was found and can-

nulated and through it a cholangiogram demonstrated the entire intraphepatic biliary system. The patient's response to the operation was good. The pathologist's report on the liver specimen was: subacute cholangitis and biliary cirrhosis, grade I.

Postoperatively the patient's course was complicated by a sterile serosanguineous left pleural effusion which accounted for a mild febrile reaction through her twenty-second postoperative day. On the fifth postoperative day, the patient passed a dark stool and on the sixth day, urobilinogen appeared in the urine. Pruritis subsided almost immediately and the jaundice receded gradually. An icterus index was reported as 22 units 2 weeks after operation. She was discharged on her twenty-fifth postoperative day.

When seen 6 months after operation, the patient had gained 14 pounds. Her urine and stools were normal in color as were her skin and scleras. Her liver was palpated at 5 centimeters below the costal margin and had a firm, rounded, somewhat tender edge. Eighteen months postoperatively, the patient had gained 30 pounds in weight; she presented no evidence of biliary obstruction. A total serum bilirubin was 0.1 milligram per cent. Occasional transitory episodes of "indigestion" were described which could be avoided by a low fat diet. Her liver edge had receded somewhat but was still mildly tender to pressure.

This woman presented no difficulties until 3 years after cholecystectomy. Six years after her original operation, re-exploration was required for signs of biliary obstruction, at which time a diagnosis of obliterative cholangitis was made. Admittedly this condition is relatively uncommon and, more often than not, if the right upper quadrant is explored, sufficient duct is discovered to proceed with one of the more physiologic methods of biliary reconstruction. However, if such a diagnosis is based on a thorough evaluation of the individual circumstances, the decision to carry out an intrahepatic cholangiojejunostomy may be made much earlier with obvious benefit to the patient.

DISCUSSION

Indications and contraindications. It is generally stated that the most consistently satisfactory method of repairing a stricture of the common hepatic or common bile duct is to excise the fibrotic area and approximate the ends of the duct by a careful mucosa-to-mucosa anastomosis over some type of supporting tube.

Unfortunately, many of the problems of secondary biliary tract surgery are much more complicated. Oftentimes, finding the 2 ends of the duct which are to be brought together becomes a very formidable problem. This difficulty may be magnified manyfold because of further scarring, obliteration of landmarks, and distortion of anatomy each time the operator is forced to re-explore such a patient. Lahey has emphasized that with each unsuccessful attempt at duct repair the chances for a satisfactory and lasting outcome progressively diminish.

In the hands of some operators a greater percentage of duct ends are found and approximated than in others. Lahey and his associates were able to find suitable duct for simple end-to-end closure in a majority of 280 cases explored, frequently by reclaiming the distal end of the duct from the head of the pancreas. Other surgeons, notably Walters and his associates have stressed the use of a choledochoduodenal or hepaticoduodenal anastomosis, and have, in fact, shown it to be better in their hands than the end-to-end anastomosis.

When the operation of intrahepatic cholangiojejunostomy was originally described, it was stated that this procedure was indicated in cases of extensive obstruction of the extrahepatic biliary system when restoration of continuity could not be accomplished by the usual methods. Clearly, it is a matter of judgment, skill, and, particularly, experience on the part of the operating surgeon that determine the approach which will offer the greatest assurance of success. We are not in disagreement with those who are able to find sufficient duct and by mobilizing the duodenum are able to bring the ends together; nor are we suggesting that the intrahepatic approach should succeed the choledochoenteric or hepaticoenteric anastomosis whenever it is reasonably possible to find a good cuff of common bile duct or common hepatic duct in the hilus of the liver. Our debate is with those who would sacrifice valuable time as well as valuable hepatic reserve in numerous efforts to establish biliary flow by the usual procedures when in their hands one or more attempts to do so have failed.

Intrahepatic cholangiojejunostomy should not be reserved until progressive deterioration, extensive biliary cirrhosis, portal hypertension, and hepatic failure have occurred. It should not be withheld until the patient is in such poor condition that even if successfully accomplished, reasonably normal health is denied him because of the progressive liver damage already incurred. The timing of this procedure, as in many operations, may be very important.

It is our intention to present this operative procedure as a logical and reasonable approach which may follow in proper sequence as an attempt to re-establish the biliary-enteric continuity in the event of failure of other, perhaps more physiologic, procedures.

Our own experience and that of others who have published their experiences with this operation would bear out the contention that although this is a formidable procedure, it is not unusually difficult to accomplish. In fact, because of the presence of less scar tissue and fewer adhesions in the left upper part of the abdomen, as compared to the right, and because after exposure of the intrahepatic duct the accessibility of structures facilitates the performance of an accurate mucosa-to-mucosa anastomosis with the jejunum, it is our impression that this procedure is less difficult than one which requires tedious, careful dissection and anastomosis of structures deep in the hilus.

Our experience with intrahepatic cholangiojejunostomy has been limited to cases of benign obstruction of the extrahepatic biliary tree. Waddell and Burbank, Sawyer, and Beal, however, have reported a combined total of 6 patients in whom this procedure was employed palliatively for biliary obstruction caused by extensive malignant disease with primary or secondary involvement of the extrahepatic ducts. It was pointed out that suitable sidetracking operations were unfeasible in these cases because of the extensiveness of the lesion. Three of Sawyer's 4 patients were completely relieved of jaundice and pruritis. All succumbed to their disease, however, in from 10 days to 2 months after operation. Waddell and Burbank's patient lived for 13 months postoperatively. For 8 months, he was free from jaundice, although this patient did have repeated bouts of cholangitis. Beal's patient lived almost 5 weeks after operation, but although there was evidence of biliary flow postoperatively, the patient's jaundice did not recede.

We are inclined to believe that the intrahepatic cholangiojejunostomy should not be employed for the relief of jaundice due to primary or secondary malignant disease of the extrahepatic biliary system. However, it is difficult not to agree with Waddell and Burbank that under certain conditions, the operation could be judiciously applied with great benefit to the patient.

Technique of operation. The detailed technique employed in this procedure has been adequately described in earlier communications (7, 8). A V-shaped bilateral subcostal incision extending farther to the left than to the right has given satisfactory exposure in most cases. However, occasionally we have utilized an incision which is placed directly over the left costal margin. In this instance, the muscular attachments are freed from the left costal arch and by dividing the sixth and seventh costal cartilages anteriorly and the ninth and tenth costal cartilages laterally, and severing the ends of the intervening sixth, seventh, and eighth ribs, the costal margin may be reflected upward as a flap. In certain patients, notably those with a narrow costal angle, this incision may give more adequate exposure of the left upper quadrant without opening into the thorax.

It has been our practice to use a Roux segment of jejunum for the biliary-enteric anastomosis. It is thought that this is a more satisfactory method of defunctionalizing a segment of bowel than the jejunal loop with proximal enteroenterostomy. Our experience to date has not altered that impression.

In our last 4 cases, a cholangiogram was made at the operating table just prior to the construction of the biliary-enteric anastomosis. By injecting 20 cubic centimeters of 35 per cent diodrast into a catheter placed in the exposed intrahepatic duct, it is possible to outline the entire intrahepatic biliary system. Two purposes are served by this maneuver: (1) we are able to identify accurately the

major left hepatic duct so that the largest possible anastomosis may be made between the biliary system and the bowel, and (2) we are able to predict if both the right and left hepatic lobes will drain through the exposed duct. In 3 of our 4 patients, both of these facts were elicited in each instance by this procedure. In 1 case, a technical error in roentgenography was responsible for the failure. Massie has suggested that a cholangiogram be made before the left lobe is removed. He states that if the obstruction is above the point of juncture of the major hepatic ducts, the 2 lobes would be isolated and a successful outcome would depend upon preserving as much of the left lobe as possible. It has been emphasized in a previous report (7) that the extrahepatic obstruction is rarely, if ever, high enough to block the confluens of the right and left major hepatic ducts. Our clinical experience with operative cholangiography would seem to substantiate this point.

Communication between the right and left lobes in these cases probably does occur in largest measure through the blind stub of the common hepatic duct; but when the intrahepatic ducts have been abnormally distended over a prolonged period of time, the minor communicative channels which have been shown to exist in the caudate lobe may assume an unusual degree of importance.

In view of the simplicity of the technique and the value of the information to be gained, it is suggested that operative cholangiography be utilized as a valuable adjunct in all of these cases.

SUMMARY

Five cases are reported in which an intrahepatic cholangiojejunostomy with partial hepatectomy was employed for the relief of extensive extrahepatic biliary obstruction. This brings to 23 the total number of reported cases to date.

There was 1 postoperative death which was due to a fatal hemorrhage from a ruptured esophageal varix. One patient with an external biliary fistula which drained intermittently survived almost 13 months after operation but was not greatly benefited by the procedure. A third patient has been alive 40 months following operation but because of previous prolonged hepatic injury and consequent biliary cirrhosis, her jaundice has not entirely receded and biliary flow is not completely free. A fourth case was followed for 31 months, during which time there was no objective evidence of biliary obstruction. The fifth patient is entirely well after a period of 18 months and presents no stigmas of her previous disease except for a mild subsiding hepatitis.

Intrahepatic cholangiojejunostomy has been employed by the authors for extensive benign obstruction of the extrahepatic biliary system when the usual methods of re-establishing biliary-enteric continuity have proved to be inadequate. We have not used this approach as a palliative procedure for primary and secondary malignant obstruction of the extrahepatic biliary tree.

It has been emphasized that this operation should not be reserved until biliary cirrhosis and its attendant sequelae have occurred, but rather it should be utilized in its logical sequence in the event that other, perhaps more physiologic, procedures have proved to be unsuccessful.

Operative cholangiography has been shown to be an invaluable adjunct in the performance of intrahepatic cholangiojejunostomy.

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EDITORIALS

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SIGNIFICANCE OF PREOPERATIVE WEIGHT IN THE CHOICE OF OPERATION FOR DUODENAL ULCER

THE program chairman of a surgical society has little difficulty in getting equally distinguished surgeons each of whom is eager to champion his particular operation for duodenal ulcer. If the discussion is heated, and it may well be, the audience enjoys the debate, but it is doubtful if either side succeeds in making many "converts," especially among the older, more experienced surgeons. Furthermore, many young surgeons have already become blind devotees of a particular operation for duodenal ulcer which, mastered during their period of training, is used routinely without due regard to its indications or limitations. The lone skeptics all too frequently are the nonsurgical members of the audience who have been responsible for the long term postoperative care of those patients having had one of the "ideal operations." While the surgeons emphasize the operative mortality rate and the incidence of recurrent ulceration or hemorrhage, these physicians are perplexed by the new symptoms and problems that many of their patients have developed, regardless of the type of operation performed.

The cumulative effect of the original disease, in combination with a variety of digestive symptoms resulting from the mechanical and anatomic alterations of surgery, frequently results in detriment to the body weight and, if severe, may prove to be the patient's major problem. While the over-all average loss of weight in a reported series having a particular operation may not appear significant, a considerable number of those patients who lost weight contributed a lion's share to this "insignificant" loss. These are the patients whose nutritional problems may seriously handicap their physical and economic well being. In these instances, the preoperative nutritional status as indicated by body weight has proved to be of considerable prognostic value as to their postoperative weight trends following either conservative or radical procedures.

The ideal weight for sex, height, body build, and age either computed by formula or from life insurance tables should be determined preoperatively in every patient with duodenal ulcer. A customary 5 pound range either above (maximum) or below (minimum) the ideal weight is allowed. Everyone will admit that a surgical procedure need not return a given patient to an overweight status. Neither should it hold the patient below his minimal ideal weight, which according to life insurance weight tables is invariably on the lean side. A survey of several hundred patients

1 to 6 years after an extensive Hofmeister gastric resection, vagotomy with gastroenterostomy or a conservative resection (Billroth I), suggested a relationship of the late postoperative weight to the type of surgical procedure as well as the preoperative weight.

A comparison of the preoperative weight to their calculated ideal divided the patients into one of three groups: Group I, those at or above their calculated ideal weight; Group II, those who at one time were at or above their ideal weight but were below this level preoperatively; and finally, Group III, those patients who had never attained their ideal weight at any time in their life.

The late postoperative weights in Group I showed that approximately two-thirds or 68 per cent held their ideal weight regardless of whether a radical resection or a vagotomy and posterior gastroenterostomy had been performed. Of those patients actually above their maximum weight in this group preoperatively, 4 out of 5 realized their ideal weight after operation regardless of procedure. If their weight was less than the maximum, yet in the optimal range, a discrepancy in favor of a conservative procedure became apparent. Only 1 out of 3 held their ideal after a radical gastrectomy in contrast to 2 out of 3 having posterior gastroenterostomy and vagotomy who sustained their ideal weight postoperatively.

In Group II, which contained many of the patients who had lost weight because of pyloric obstruction, the postoperative weights were in general quite disappointing, especially in those having a radical resection. These patients had about 1 chance in 10 of regaining their ideal weight following radical resection. Here the benefit of the conservative procedures became quite apparent since more than 1 out of 3 patients had regained their ideal weight.

In Group III, as might be expected, practically no patient ever gained up to his ideal regardless of the type of surgical procedure employed.

The surgeon has the responsibility of maintaining an adequate nutritional status for the patient after surgery for duodenal ulcer. Unsatisfactory weight trends should be anticipated in the majority of patients whose preoperative weight levels are below their ideal weight. Since the weight trends in this group of patients are related to the procedure employed, consideration should be given to the control of the acid factor by means other than a radical gastric resection.

Data on the preoperative as well as the postoperative weight in relation to the ideal would seem desirable in the evaluation of the effectiveness of any operation for duodenal ulcer. Perhaps the percentage of patients in the various categories in any reported series might well condemn or praise a particular operation for duodenal ulcer. The patient's preoperative weight in relation to the calculated ideal should be one of the deciding factors in selecting the operation most likely to insure satisfactory nutrition postoperatively.

ROBERT ZOLLINGER.

ABNORMAL CARDIAC RATE, RHYTHM, AND CONDUCTIVITY IN THE OPERATING ROOM

THE causes of sudden hypotension during the course of an operation are many and varied. A reduction in the effectively circulating blood volume from blood loss or peripheral vasodilation is the commonest cause of acute hypotension and it is usually readily apparent to the surgeon and anesthetist. Abnormalities of rate, rhythm, and conductivity such as supraventricular tachycardia, auricular fibrillation or

flutter, ventricular tachycardia, and atrioventricular block can produce acute hypotension, and unfortunately these are not always recognized as promptly by the operating team as is desirable. Most of these abnormalities can be prevented by the adequate preparation of the patient, the judicious use of preanesthetic drugs, and the careful conduct of the anesthesia. Most can be managed satisfactorily if promptly recognized and intelligently treated.

Irrespective of the pathogenesis of acute hypotension, there is a tendency to increase the rate of administration of intravenous fluids and blood and to give a moderate to large dose of a vasopressor drug. In the presence of functional disturbances of cardiac action, these measures can be deleterious rather than beneficial. Overloading the venous circulation with fluids when cardiac efficiency has been reduced by a rapid rate, arrhythmia, or block can produce a further reduction in cardiac efficiency and an intractable pulmonary edema.

The most important aspect of these functional disturbances of cardiac action in the operating room is prevention. The next most important is prompt recognition. If this cannot be accomplished within a few seconds by palpation of the pulse and/or auscultation of the heart, an electrocardiogram should be obtained on a direct writing electrocardiograph. Such an instrument should be immediately available in every operating suite. Numerous members of the operating suite personnel should be familiar with the proper application of the leads to the patient and the proper operation of the instrument. For patients in whom these disturbances can be anticipated in spite of careful preparation and prophylaxis the electrocardiograph can be attached before induction of anesthesia. Oscilloscopes are commercially available which provide a constant display of cardiac electrical activity for the benefit of the anesthetist.

If these disturbances are to be promptly and intelligently managed, surgeons and anesthetists will have to be more familiar with the interpretation of the electrocardiogram than they are at the present. It should be possible for them to recognize abnormalities of rhythm, rate, and conduction. It also is desirable that they become familiar with the use of the few drugs that are of tremendous value in the treatment of these sometimes fatal functional disturbances.

WILLIAM D. HOLDEN.

THE SURGEON AT WORK

A METHOD OF MANAGEMENT OF THE DUODENAL STUMP AFTER GASTRECTOMY

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SEVERAL years ago, in order to make gastric resection easier and safer, interest was revived in the procedure of duodenostomy and the operation was modified to minimize the dangers of duodenal fistula. Sufficient time has elapsed since then so that, in addition to the cases reported in this paper, many isolated instances in which the procedure has been used have been called to the authors' attention. Because of this interest, it seems worth while to discuss the technique of the operation and the postoperative management of the patient.

Closure of the duodenal stump after partial gastrectomy, particularly for duodenal ulcer, is frequently a serious technical problem. Besides an ineffective closure of the stump, other important hazards of removing large posterior wall ulcers include damage to the pancreas with the production of fulminant postoperative pancreatitis and of section or ligature of the common bile duct. It is recognized, therefore, that the leakage of duodenal contents into the peritoneal cavity must be prevented and also excessive manipulation about the pancreas and biliary ducts must be avoided.

Some surgeons maintain that all duodenal ulcers can be excised and the duodenum closed safely beyond the point of dissection. It is certain that if this advice were followed by every surgeon who performs gastrectomy the death rate from this operation would be so high that it would be discarded in favor of some less lethal procedure. Fortunately, most surgeons recognize their technical limitations and, faced with a difficult and dangerous dissection, choose some other alternative. These alternatives include one of the various types of resection for exclusion, a two stage resection, or vagotomy and posterior gastroenterostomy.

Thus, in most instances, the surgeon in some fashion can avoid a dangerous dissection beyond the pylorus. This paper is not concerned with the selection and employment of these alternative procedures, nor with their merits and disadvantages. There will remain, however, a few cases in which they cannot be used. Particularly when the indication for operation is acute massive hemorrhage from a duodenal ulcer, the actual ulcer bed should be exposed to secure control of the bleeding. In other cases, and not infrequently, the surgeon commits himself to a gastric resection and unhappily finds that the duodenum is much more difficult to mobilize than he had expected. Here, either the hazards of deep dissection must be faced or a duodenostomy must be accepted.

A historical review of the use of duodenostomy had led us to believe that this operation in the past was occasionally life-saving, but also frequently fatal, solely because of the established duodenal fistula. Modern methods of electrolyte and fluid balance control have, of course, greatly reduced the mortality from such a fistula so that duodenostomy is correspondingly safer in these days. However, we have been concerned with the development of a method that should make the operation as safe as possible and hence could be recommended for general use.

It is impossible to know how many surgeons have tried and abandoned duodenostomy in these circumstances. Certainly, until recently, it has never received unqualified approval from any surgeon. A duodenostomy apparently was made first by Langenbuch in 1880. He constructed a duodenal fistula for feeding purposes. This same procedure had been suggested nearly simultaneously by Billroth (16). A number of surgeons, including Bassett, later carried out this operation. Neumann, in 1909, inserted a catheter into a perforated ulcer of the duodenum. This procedure still is carried out by some surgeons.

The use of duodenostomy after gastric resection was approached by Felsenreich in 1933 when he created a localized cavity around an insecure

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closure of the duodenum and placed rubber drains into this cavity. In 3 of his cases so treated fistulas developed, and all closed within 3 weeks. In 1936, Friedmann employed catheter duodenostomy to decompress the duodenum in 2 cases in which insecure closure of the duodenal stump followed gastrectomy; in both cases the fistulas closed promptly.

It seems apparent that the reported successes of duodenostomy must have been equalled by disasters, either from peritonitis or electrolyte depletion, since the operation never was accepted as a standard procedure. For example, in Bruusgaard's comprehensive study, it is mentioned only to be condemned. On the other hand, several American surgeons have used it occasionally with generally satisfactory results without, however, publishing any reports. Representative of this group are Smithwick, Whipple, and Waugh.

We personally became interested in this operation in 1946. At that time it seemed probable that the objections raised to its use could be combatted satisfactorily. Leakage into the peritoneal cavity might be prevented by careful closure of the duodenum about a catheter. Electrolyte depletion could be prevented entirely by modern methods. This depletion is not difficult to correct in the usual case by intravenous fluids and electrolytes. However, it can be extremely serious if there should be postoperative stomal obstruction. By the use of concomitant jejunostomy catheters, the fistula should be controlled completely.

As our experience has increased (13, 14), we have become much more impressed with this method. Meanwhile, other authors, including Priestley, Ross and Warren, and Hoerr have endorsed it. Hoerr has extended the applicability of this procedure to some cases that could have been handled in other ways and has found it extremely helpful as well as devoid of danger.

In the past 5 years, we have used this method in 10 instances, or in approximately 3 per cent of all gastric resections for duodenal ulcer. Increasing confidence in the method has led us to extend its applicability, and its use has reduced the duration of hospitalization after operation. It seems probable that it should have been used twice as frequently as it was. Obviously, it is not used when other methods apparently will succeed, but we find it is far safer than an insecure closure of the duodenal stump or a deep dissection along the head of the pancreas.

The method essentially is not difficult. After the usual gastric resection for ulcer, a catheter is sutured tightly into the open end of the duodenum which is then closed about it. The catheeter, together with a cigarette wick, is brought out through a subcostal incision. Finally, a double jejunostomy is performed, according to the method of Allen and Donaldson. The abdomen, as it appears at the close of the operation, is shown in Figure 1. Several details, however, require further discussion.

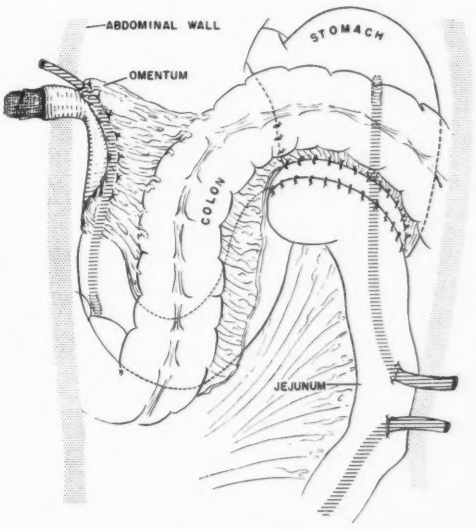

Fig. 1. Technique of duodenostomy.

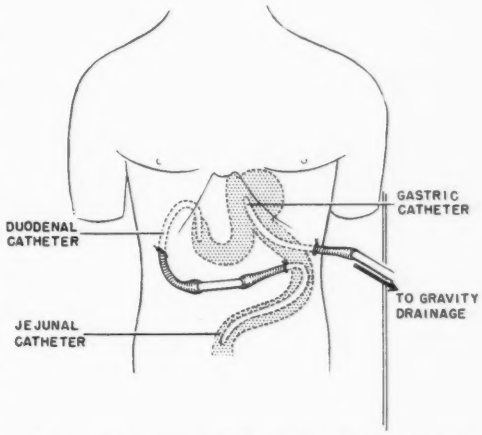

Fig. 2. Management of duodenal catheter. The duodenal and jejunal catheters are connected 48 hours after resection.

TABLE I.—SUMMARY OF 10 CASES

Patient No. Date of operation	Type of ulcer	Indication for operation	Type of operation	No. of days duodenal catheter retained	Postoperative complications	No. of postoperative hospital days	Result
44550 5-25-48	Duodenal	Obstruction	Two stage gastrectomy	14	None	18	Recovered
522259 6-17-48	Duodenal	*Massive hemorrhage	75 per cent gastrectomy	21	None	24	Recovered
557860 10-27-49	Duodenal	Massive hemorrhage	75 per cent gastrectomy	17	Stomal obstruction	27	Recovered
701557 5-22-50	Duodenal	Obstruction, perforation with abscess	75 per cent gastrectomy	22	Pancreatic abscess	51	Recovered
448176 6-8-51	Anastomotic	Pain	Gastric resection, jejunal resection, enteroenterostomy	12	†Local peritonitis	18	Recovered
754345 10-11-51	Duodenal	Obstruction, posterior perforation	75 per cent gastrectomy	12	Bleeding from suture line	16	Recovered
761666 1-5-52	Duodenal	Obstruction, posterior perforation	75 per cent gastrectomy	10	None	14	Recovered
7959 5-29-52	Duodenal	Massive hemorrhage	‡Bancroft	14	None	17	Recovered
783461 8-8-52	Duodenal	Hemorrhage	75 per cent gastrectomy	15	Stomal obstruction	21	Recovered
796099 12-8-52	Duodenal	Massive hemorrhage	75 per cent gastrectomy	9	**Leakage around duodenal catheter	14	Recovered

*On 6-17-48 had 75 per cent gastrectomy with duodenum turned in proximal to ulcer for massive hemorrhage. Again bled massively on 6-22 and 6-23. On 6-23 had ligation of gastroduodenal artery and duodenostomy.
†Slight peritoneal reaction for 48 hours after removal of catheter.
‡Three days after Bancroft operation for massive hemorrhage again bled massively. Ligation of gastroduodenal artery and duodenostomy performed on 6-3-52.
**Two days after operation, duodenal drainage occurred about the catheter. Sump drain inserted beside cigarette wick with prompt relief on suction.

1. Extent of dissection. It is preferable to carry the dissection as short a distance as possible beyond the pylorus. This is particularly important since damage to the pancreas is reduced correspondingly. Furthermore, a longer section of duodenum is available to close about the catheter.

2. The catheter. A No. 16 whistle-tip catheter is preferred. The catheter must not be stiff, yet not so soft that it will kink easily. A sinus tract produced by a larger tube takes longer to close, while smaller catheters tend to be occluded by the sutures. So far, no harmful effects from the inlying catheter have been noted, even when it is in apposition with the ulcer bed. It is obvious, however, that all bleeding must be controlled completely before the closure.

3. Duodenal closure. After the catheter is sewn to the duodenum, it is important that a watertight closure of the duodenum be obtained about it. Whether this can be secured best by purse-string or plicating sutures will depend upon individual circumstances. Leakage is most likely at the posterior margin of the open duodenum, particularly when the pancreas is densely adherent at this spot. If possible, two layers of catgut sutures are used. Effectiveness of the closure may be tested by irrigation of the catheter with a rubber bulb syringe and salt solution while the distal duodenum is compressed with the finger. Finally the end of the duodenum and the catheter are covered generously with omentum.

4. Supplementary drainage. A cigarette wick is placed in Morrison's pouch to be brought out through the abdominal wall with the catheter. This extra precaution has always been used since a disoriented patient pulled out a catheter 4 days after operation before a sinus tract was established. In the only other instance in which duodenal drainage occurred about the catheter it was noted immediately and controlled by the insertion of a small sump drain.

5. Site of drainage. If a vertical incision has been employed, the catheter is brought out through a stab wound below the right costal margin. If the incision is transverse, the catheter is brought through the lateral end.

6. Double jejunostomy. We believe that a double jejunostomy should always be carried out. If stomal obstruction does not develop after operation, this precaution is not absolutely necessary since loss of fluid and electrolytes from the fistula can be corrected by intravenous administration. However, these jejunostomies are invaluable when an obstruction of the stoma takes place.

Postoperatively, the duodenostomy catheter is allowed to drain by gravity for 48 hours. Since the drainage bottle is placed on the floor, a slight negative pressure is created in the duodenum and the collection of about a liter of fluid will result in each 24 hour period. As soon as intestinal peristaltic activity is demonstrated by auscultation, the catheter from the duodenum is connected to the lower jejunal catheter by a glass tube (Fig. 2) to allow complete absorption of the duodenal contents. If peristaltic activity is delayed over 48 hours, an air vent is placed in the duodenal drainage tube at the level of the duodenum so that less fluid is lost from the fistula.

In the usual case, the duodenostomy catheter can be clamped off on the eighth day and removed 2 days later. Drainage usually ceases almost immediately. The jejunostomy catheters and the cigarette wick are removed on the following day and the patient is discharged shortly thereafter. If postoperative complications should ensue, removal of the tubes should be postponed, particularly in the case of stomal obstruction, when they are retained until barium studies show adequate function of the anastomosis.

The results have been quite satisfactory. The 10 patients treated by us in this fashion in the Massachusetts General Hospital have all recovered. Postoperative complications included stomal obstruction, secondary hemorrhage from the anastomosis, leakage around the duodenal catheter, and pancreatitis. Except for the 1 case of pancreatitis in which repeated drainage was required, there were no particular problems of management. The pancreatitis, we believe, was due to a wide mobilization of the head of the pancreas in a fruitless attempt at closure. Details of the various cases are summarized in Table I.

SUMMARY

A method for the production and management of a catheter duodenostomy is discussed. This procedure contributes to the safety of gastric resection for duodenal ulcer. Control of the duodenostomy is achieved by simultaneous jejunostomies for gastric decompression and jejunal alimentation. The details of 10 cases treated successfully by this method are considered.

ADDENDUM. Since submission of this article for publication 3 additional cases have been treated in a similar manner, and 4 by decompression of the duodenum by catheter just distal to the line of closure. All 7 recovered uneventfully.

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THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE second edition of *Operative Gynecology*[1] by Richard W. Te Linde is a meticulous revision of an authoritative gynecologic text. The author takes cognizance of major surgical gynecologic advances which have evolved since publication of the first edition. New chapters have been incorporated on "The Use of Pessaries," "The Surgery of the Double Uterus," "Culdoscopy," "Carcinoma of the Cervix in Situ," and "Sarcoma of the Uterus." Note is taken of the advances in chemotherapy and antibiotic therapy.

The description of the technique of the Wertheim type of radical hysterectomy has been rewritten and is accompanied by an excellent set of new illustrations. A considerable change is evident in the author's attitude toward vaginal hysterectomy; it is noted that he has greatly increased the use of vaginal removal of the uterus when no prolapse or only a slight prolapse exists. It is interesting to see that he continues to consider the Watkins transposition operation a satisfactory procedure for the treatment of selected cases of prolapse of a healthy uterus and of cystocele in patients approaching or past the menopause. He mentions the use of fascia obtained from the sheath of the rectus in the treatment of vaginal prolapse. The Marshall, Marchetti, and Krantz operation for stress incontinence is described and illustrated but suprapubic procedures for that disorder are not included. The author states that he has come more and more to the conclusion that almost all vesicovaginal fistulas should be closed by the vaginal route.

The chapter on anesthesia is changed considerably. It appears that pentothal alone or pentothal with curare are the favored anesthetic agents. Cardiac arrest is discussed but the use of the defibrillator is not described in its treatment. The author continues to use No. 2 plain catgut for closing the peritoneum at laparotomy, single or double figure of 8 No. 1 chromic catgut for approximating the abdominal fascia, and stay sutures. He keeps his patients on liquid diets for 5 days after operation and is of the opinion that 10 days postoperative bed rest are advantageous. Although he states that published reports seem to indicate that prophylactic anticoagulant therapy is of value in preventing postoperative thrombophlebotic complications, he reserves it for cases in which there appears to be a greater than average chance of phlebitis or embolism.

In addition to the new chapters and the changes mentioned there are many other alterations both in the illustrations and in the text. The illustrations and descriptions of the operative techniques make the book an excellent surgical atlas. It offers concise descriptions of pertinent surgical-anatomic relationships and discussions of the entities requiring surgery. There are relatively few references to the literature since 1946. The text is an invaluable handbook for the young gynecologic surgeon; it is an equally valuable reference for the experienced gynecologist and the general surgeon who does gynecologic surgery. JOHN W. HUFFMAN.

FOR the first time, a single, compact, simplified text has been written encompassing the clinical, biologic, pathologic, and therapeutic aspects of atomic energy. Doctor Sears in *The Physician in Anatomic Defense*[2] has put together in brief readable form the pertinent essentials of the physics of the atom gathered together from various sources, both personal and written. The mechanism and hazards of the atomic bomb, the resulting syndromes and their therapy are dealt with at some length. Finally, methods of civil defense and the importance of the medical department in defense is considered.

This 300 page text is easy to read, logical in arrangement, and very instructive. With the atomic age upon us this book should be of immediate interest to all medical men. HAROLD L. METHOD

THE book *Thoracic Surgery and Related Pathology* of some 650 pages coming from the faculty of the Yale University School of Medicine was "written to provide a compilation of available knowledge in the field of thoracic surgery, with particular attention to those basic aspects of anatomy, physiology, and pathology that are essential to a comprehension of this complex subject." This is not a textbook of surgery for it actually contains little of technical detail. It is not a textbook of pathology or anatomy, neither is it a textbook on medical diseases of the chest. It is actually a very interesting combination of all of these. It takes up a pathologic condition by

[1] OPERATIVE GYNECOLOGY. By Richard W. Te Linde. 2nd ed. 902 pages, with 409 figures and 7 color plates. $20.00. Philadelphia, London, Montreal: J. B. Lippincott Co., 1953.

[2] THE PHYSICIAN IN ATOMIC DEFENSE; ATOMIC PRINCIPLES, BIOLOGIC REACTION AND ORGANIZATION FOR MEDICAL DEFENSE. By Thad P. Sears, M.D., F.A.C.P. With a foreword by James J. Waring, M.D., M.A.C.P. 308 pages, with 53 illustrations. $6.00. Chicago: The Year Book Publishers, 1953.

[3] THORACIC SURGERY AND RELATED PATHOLOGY. By Gustaf E. Lindskog, B.S., M.A., M.D., F.A.C.S., and Averill A. Liebow, B.S., M.D. 644 pages, with 285 illustrations. $15.00. New York: Appleton-Century-Crofts, Inc., 1953.

telling what it is, what is important in producing it or bringing it about, and it discusses what to do about it in the way of treatment. If treatment is surgical, an account of what is accomplished at surgery and what can be expected by surgical treatment is given. It, therefore, really represents a digest of each subject as it is viewed in the light of present day opinion. An honest attempt has been made to present the essence of opinions both past and present and the result is remarkably up to date. Thus I believe the authors succeeded well in their purpose.

Condensation of an enormous mass of material such as is available in the realm of chest diseases and assigning the proper value to the changing concepts and opinions inherent in a rapidly developing subject is a very challenging task indeed. The authors have undertaken it in a conscientious manner and have achieved it without apparent bias.

The arrangement of the subject matter is logical, and the authors have included sections on respiratory function, and chapters on postoperative pulmonary complications as they relate to chest surgical patients, as well as to the pulmonary complications that may follow surgery in other anatomic fields.

In discussing pulmonary tuberculosis the writers have prepared chapters on surgical procedures that are considered obsolete or obsolescent. They consider this valuable chiefly as background material important in framing the present concepts of therapy. The chapters on therapeutic pneumothorax, oleothorax, phrenic nerve paralysis, pneumonolysis and apicolysis and cavity drainage, which aggregate some 40 pages, fall into this category and could perhaps have been shortened. They are nonetheless pertinent to the recent past.

The discussion of the heart and pericardium occupies 100 pages.

Supplementing the text and appended to each chapter is a list of selected bibliographic references.

The book is well organized, well bound, and clearly printed on good paper. The illustrations are generously scattered throughout the text, and run the gamut of types. Whereas they are always pertinent to the text certain criticisms can nevertheless be levelled at them.

Use of corrosion models to depict various aspects of the bronchovascular arborization is helpful, when applicable. Whereas such models are beautiful pieces of work and represent much labor, their complexity is often confusing when presented in a photograph. The actual model, when in hand, can be turned to show spacial relations clearly, but this advantage is lost in the photograph which is perforce a single projection.

Photographs of specimen and fields of operation are very frequently employed. There is indeed an admirable collection of pathologic material which does much to provide authenticity to the text. Lack of contrast and the presence of confusing highlights, factors so difficult to eliminate or control, tend often, however, to detract from the lucidity of these as illustrative material.

Perfect specimens and perfect reproductions are indeed very rare for many and very valid reasons. Unfortunately the use of confusing or complicated illustrations tends to diminish rather than enhance the appreciation of the point to be grasped, and leaves the reader still dependent upon the legend rather than the illustration. One gets the impression, therefore, that many of the illustrations labor much to discharge their function.

This book is a very welcome addition to library shelves that deal with thoracic disease because it has a very real place to fill. It represents an effort to abridge the knowledge in this field basing it primarily on fundamentals of anatomy, pathology, and physiology, but invested with a surgical slant. Thus, for the student it can serve as a primer, for the casual medical reader it will satisfy the curiosity, yet for the more experienced internist or surgeon it can be used as a condensed expression of authoritative opinion, which can easily be amplified by following the appended bibliographic suggestions.

The authors should be congratulated for having had the foresight to prepare this book along these lines.

HIRAM I. LANGSTON.

IN THE monograph *Stress Incontinence in the Female*[1] the author set himself the task to gather and to review critically the pertinent literature on this subject. He has admirably succeeded in this task and the resulting 149 page book will be very useful to those interested in this problem.

The subject matter is divided into 7 chapters which deal with the definition and classification of stress incontinence, the embryology, and the anatomy of the urethra and bladder, the physiology of urination and continence, the etiology of stress incontinence, its diagnosis, and treatment. The chapter dealing with the embryology, histology, and gross anatomy of the urethra and its supporting structures is clear and beautifully illustrated. The many opinions on the physiology of micturition and continence presented in the third chapter are quite revealing of the uncertainty and confusion which still surrounds our knowledge of these matters. The portions of the book which discuss the etiology of stress incontinence, its operative and nonoperative treatment are thorough and well presented. The most important surgical procedures in use today and their particular indications for the relief of urinary stress incontinence are fully described and are accompanied by illustrations which clearly demonstrate each step of the operation. The author correctly states, I believe, that the results of the nonoperative treatment of stress incontinence in recent years proposed with so much enthusiasm has so far not quite measured up to the original expectations, and that its true worth still remains to be evaluated.

The final paragraph of the book emphasizes the fact that many questions concerning urinary stress

[1] STRESS INCONTINENCE IN THE FEMALE. By John C. Ullery, M.D., F.A.C.S., F.I.C.S. 149 pages, 82 illustrations. $6.75. New York: Grune & Stratton, 1953.

incontinence in women are as yet unanswered, and that much remains to be explored. This should be both sobering and stimulating to the investigator of this problem. A few small errors in print and in the bibliography do not seriously detract from the value of this monograph. S. RICHARD MUELLNER.

FAVORABLE comments may be readily made about the excellent text *Surgical Pathology*.[1] There are minimal points of difference accountable only by variations in views.

In the preface, the author elaborates on the field of surgical pathology by using the phrase "the pathology of the living." He indicates that there is a movement from the autopsy room, that pathology as a course in the curriculum and a part of the practice of surgery and of general medicine has not been replaced by the other preclinical sciences.

One brief chapter defines the objectives and the duties of the surgical pathologist. Here, there are two insignificant interpretations with which this reviewer disagrees; one, the extent of usefulness of immediate frozen section and the degree to which the pathologist may go in his interpretation; and second, his question of the value of cytologic study in patients without symptoms. In both thoughts there is a more conservative approach than that followed by this reviewer.

Two of the chapters have been written by close associates of Dr. Ackerman. Each is well known in the respective fields and each contributes adequately to the book. One is on the skin by Dr. Zola Cooper and the other on the central nervous system by Dr. David E. Smith. The first is at the beginning and the second at the end of the volume.

The intervening chapters represent the clear concise authentic style of the author. In his presentation he has followed a simple form with stress on the common and minimal emphasis on the infrequent lesions. As might be expected the inflammations, the congenital anomalies, and the neoplasms receive the most space. Trauma plays a lesser role, and less complex classifications are used. Trite phrases and cliches are avoided. There is little tendency to hedge. Theory is at a minimum; his own experience guides his hand in the composition. One can also detect the influence of several of the men with whom the essayist has been associated previously.

Gross photographs as well as some clinical pictures are used more frequently than photomicrographs. All are reproduced quite clearly. There are tables tabulating the differences in some frequent though complex entities. By them, one may distinguish the alterations more readily. The bibliographies at the end of each chapter are selected for extent of coverage and recent date.

On the physical side, the book is compact and well bound, has a fine grade of paper, and is in large distinct type with the lines extending across the whole page. The index is complete and there is a tabular listing of the various subjects covered at the opening of each chapter.

This book is recommended for thorough reading by all physicians and medical students.

M. C. WHEELOCK.

THE twenty-first edition of the well known text *May's Manual of the Diseases of the Eye for Students and General Practitioners*[2] follows the pattern originally established and still remains a text for students and practitioners.

The contents have been revised and considerable new material added including the present day beliefs on cortisone, ACTH, and antibiotics. Sections have also been added on scleral resection and retrolental fibroplasia.

Twenty-five new color plates have been added. Many of the old black and white photographs and drawings that have been in constant use for many years have been reproduced again, however, and this detracts from the appearance of the text. The book could be improved considerably by substituting new photographs for the familiar faces.

The material in the book is confined to 512 pages. It is presented in a concise systematic manner covering the subject matter clearly and adequately. It is still one of our best manuals in ophthalmology.

IRVING PUNTENNEY.

THE details of the sexual experiences drawn from the memories of 5,940 American women are given in *Sexual Behavior in the Human Female*[3] by Alfred C. Kinsey, Wardell B. Pomeroy, Clyde E. Martin, and Paul H. Gebhard. These women represented limited segments of the population as regards education, race, religious attitudes, marital experiences, residences, ages, and occupations. Many large groups of the population were not sampled. The authors deliberately chose not to use probability sampling. They also note that their sample is inadequate in many points and that the generalizations reached are least likely to be applicable to a number of groups, including large categories such as previously married females, rural groups, Catholic and Jewish women, grade and high school graduates, and laboring groups. They have not undertaken to estimate the incidences and frequencies of the various types of sexual activities in the total United States population because their sample of females is inadequate in certain large segments of that population. Despite these statements defining the limited source of the statistical material, the work bears a title which does not define such a limitation.

[1]SURGICAL PATHOLOGY. By Lauren V. Ackerman, M.D. 836 pages, 913 illustrations. $14.50. St. Louis: The C. V. Mosby Co., 1953.

[2]MAY'S MANUAL OF THE DISEASES OF THE EYE FOR STUDENTS AND GENERAL PRACTITIONERS. Edited by Charles A. Perera, M.D. 21st rev. ed. 512 pages, 378 illustrations. $6.00. Baltimore: Williams & Wilkins Co., 1953.

[3]SEXUAL BEHAVIOR IN THE HUMAN FEMALE. By the Staff of the Institute for Sex Research, Indiana University. Research Associates, Alfred C. Kinsey, Wardell B. Pomeroy, Clyde E. Martin, and Paul H. Gebhard. 842 pages, 155 illustrations. $8.00. Philadelphia and London: W. B. Saunders Co., 1953.

In the text, comparisons are made between sample groups, some of which had been stated to be inadequate. Unless the reader is acutely critical he would fail to realize that certain general statements are made which are applicable only to the sample material and, yet, which might be interpreted as general deductions regarding the sexual behavior of all American women. Statements are made which are inescapably generalizations and which are controversial to say the least.

The book eludes classification. The difficulty in assessing its biologic significance lies largely in the fashion in which the material has been arranged and the difficulty in attempting to correlate the results of the investigative sample with the much larger and dissimilar population mass. Its value as an index of morality, social behavior, and sexual patterns has been widely debated. The authors are certainly to be commended for their attempt to scientifically assess the sexual behavior of American women so that they were able to exclude such motivating factors in sexual drive as love, affection, tenderness, and selflessness not only in the sexual life of the woman, but also in that of her mate. As a contribution to clinical medicine the text offers little that is new. Most physicians are conscious of the many factors which alter such sexual behavior and of the normal and abnormal patterns which that behavior may take. They will find little in the reports of the interviews which they did not already know, namely, that certain individuals will deviate from the ethical codes of their society under the influence of different types of stimuli. The generalizations and deductions which the authors interject into their factual reports will, in many instances, arouse considerable disbelief and disapproval among physicians who are accustomed to evaluating and assessing the sexual behavior of American women.

The authors believe that they are under obligation to make the results of their investigations available to all who can read, understand, and utilize their data. It is to be sincerely hoped that their lay readers, for whom the work has been so widely publicized, will have the ability to understand the data and appropriately evaluate it. Also, that they will not have the difficulty this reviewer had in sifting the authors' reports garnered from their interviews, from their generalizations and from those which they draw from the literature regarding controversial sexual customs and behaviors.

The book is not recommended to the gynecologist, the obstetrician, nor the general surgeon, nor are they advised to recommend it as material for patient reading. If it has any value it is in its report of the sexual behavior of 5,940 upper and middle class women. Those who wish to use it as such will find considerable difficulty in distilling the accumulated facts of the authors from the fermenting mash which constitutes their presentation.

JOHN W. HUFFMAN.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

DAS ANALZAEPFCHEN IN DER GESCHICHTE DER THERAPIE. By Prof. Dr. P. Diepgen, Mainz. 44 pages, 3 illustrations. DM 4.20. Stuttgart: Georg Thieme Verlag, 1953.

DIAGNOSIS AND LOCALIZATION OF BRAIN TUMORS; A CLINICAL AND EXPERIMENTAL STUDY EMPLOYING FLUORESCENT AND RADIOACTIVE TRACER METHODS. By George E. Moore, M.D., Ph.D. 217 pages, 66 illustrations. $10.50. Springfield, Illinois: Charles C Thomas, 1953.

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THE PATHOLOGY OF TRAUMA. By Alan Richards Moritz, M.D. 2nd enl. rev. ed. 414 pages, 126 illustrations. $8.50. Philadelphia: Lea & Febiger, 1954.

DERMATOLOGIC MEDICATIONS. By Marguerite Rush Lerner, M.D., and Aaron Bunsen Lerner, M.D., Ph.D. 183 pages. $3.50. Chicago: The Year Book Publishers, Inc., 1954.

CHILDBIRTH WITHOUT FEAR; THE PRINCIPLES AND PRACTICE OF NATURAL CHILDBIRTH. By Grantly Dick Read, M.A., M.D., (Camb.). Rev. enl. ed. 298 pages, $3.00. New York: Harper & Bros., 1953.

CLINICAL CONGRESS OF AMERICAN COLLEGE OF SURGEONS

FORUM ON FUNDAMENTAL SURGICAL PROBLEMS

THE 40th Clinical Congress of the American College of Surgeons will be held in Atlantic City, November 15 to 19, 1954. The Surgical Forum sessions, which are devoted to selected papers reporting research in surgery and other fields of medical science related to the work of surgeons, will again be an important part of the scientific program of the Congress.

Authors wishing to submit reports of their research work for consideration of the Forum Committee should send the title and a 200 word abstract of each report at as early a date as possible and by May 1 at the latest. Mail abstracts to the Surgical Forum Committee, American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois. An abstract should not be limited to a statement of the objective of the experiment and the procedure followed but should clearly show results obtained. Papers presented in the Forum sessions are limited to 10 minutes each, including the showing of lantern slides if any are used to illustrate the report.

Reports of research in surgical specialties submitted for the Forum Committee's consideration have increased in recent years. This has made possible the inclusion of a Surgical Forum session for each of five surgical specialties in the programs of the last two Clinical Congresses. In recognition of this increasing interest, the Forum Committee recommended, and the Board of Regents has approved, the addition of representatives of those specialties to the Forum Committee.

The membership of the enlarged Surgical Forum Committee is:

I. S. Ravdin, Philadelphia, Chairman
J. Garrott Allen, Chicago
Bradford Cannon, Boston
Warren H. Cole, Chicago
Robert E. Gross, Boston
J. Albert Key, St. Louis
Carl A. Moyer, St. Louis
C. Hunter Shelden, Pasadena
Harris B. Shumacker, Jr., Indianapolis
Howard C. Taylor, Jr., New York
Samuel A. Vest, Charlottesville

Beginning with the 1950 Clinical Congress, the Surgical Forum Committee arranged for publication by the W. B. Saunders Company of an annual *Surgical Forum* volume which contains papers presented at Surgical Forum sessions, excepting those sessions devoted to specific surgical specialties. Members of the Forum Committee representing these specialties have felt that it is to the best interest of each specialty and the authors presenting papers in the specialty sessions to have the papers published in journals devoted to their respective specialties. The annual *Surgical Forum* volume is thus made up exclusively of the papers of all the general sessions of the Surgical Forum program.

NEW SURGICAL FORUM VOLUME IN PRESS

The *Surgical Forum* volume containing papers of the general Forum sessions of the 1953 Clinical Congress will be off the press early in April, 1954. The 138 Forum papers included in the volume are divided into 10 sections. An innovation this year is the inclusion of an introduction to each section, written by a surgeon who has worked extensively in the field covered by the section, reviewing the trends of investigation and the latest developments in that field during the past year. Although these section introductions together with the greater number of Forum papers included this year have increased very considerably the size of the new volume of *Surgical Forum*, the $10 price of the previous volumes will be maintained for the new book by the W. B. Saunders Company.

The following is quoted from a statement made by Dr. I. S. Ravdin, Professor of Surgery at the University of Pennsylvania School of Medicine, regarding the *Surgical Forum*.

"The *Surgical Forum* volume is, I believe, one of the most important of the volumes in surgery now being published in this country. It represents the work which is being done in surgical research laboratories on problems that confront the surgeon in his daily work. It further represents research into new fields of surgical endeavor. Every surgeon who wishes to keep abreast in his field should own each volume of the *Surgical Forum*."